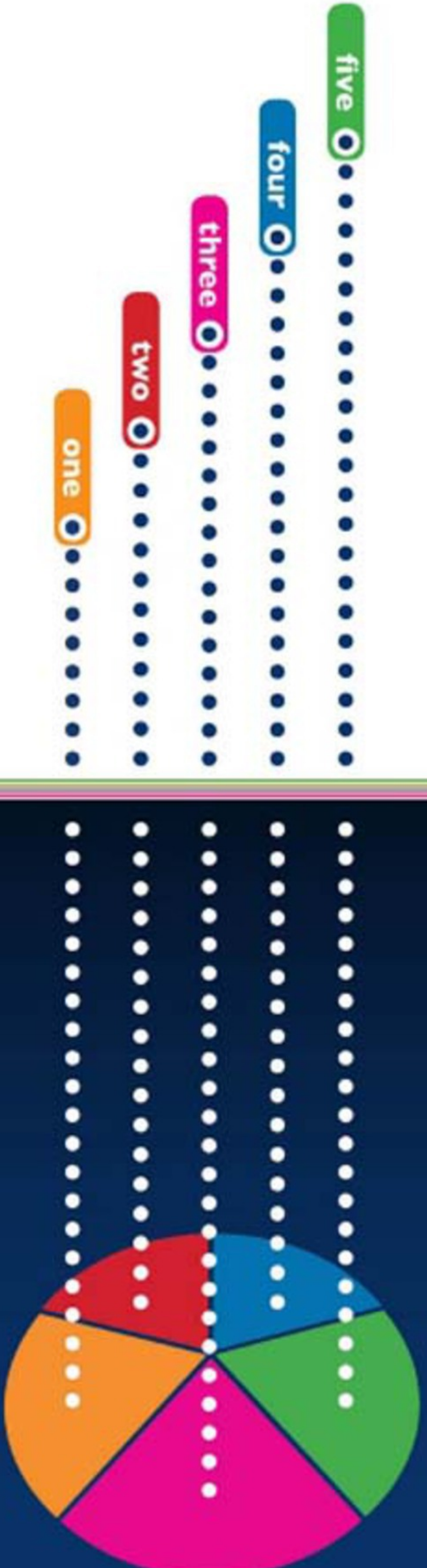
third edition

TIM HALL

PACES FOR THE MRCP

WITH **250** CLINICAL CASES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PACES for the MRCP

With 250 clinical cases

Third edition

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Preface

'What do you do, as a doctor?' is a question I often ask trainees. A range of answers emerges, unsurprisingly, as what we do is a broad collection of things. Some say we treat people. Some say we make people better, and at least in the care we give we try to, which fundamentally is a sound answer. Some say we bring together all other disciplines in the arrangement of that care, which is true to an extent, although we must be careful not to overstep the mark, for there is a range of health and other professionals in our services who can do that. Some say we are managers and, with our need to manage the care of individual patients and the care of patients at organisational levels, that is to an extent incontestably so.

Fundamentally, there is one reason for our profession, and that is to try to improve each patient's situation, to move it forward, and usually that is through treatment to help make better if not cure. That may be what we do, but the kernel of what we do in order to do that lies in fathoming out what is actually wrong with our patients.

Diagnosis is a fundamental skill for being a doctor. It is a highly complex, integrated skill that synthesises history taking, communication, examination and all of those hard-to-teach but hopefully acquired-through-experience skills of intuition and judgement and seeing things from a broader perspective. Diagnosis is key to being a doctor and a locked room to those who have not undergone medical training, because there is something about the way we have historically been trained (and the hours we have put in seeing thousands of patients, recognising herds and spotting black sheep) that allows us to do this. Heart failure and asthma treatment are hardly easy to the uninitiated, but are easy to those with a set of guidelines. Diagnosing heart failure, not singly through history or examination or radiology or echocardiography, but through complex awareness of the possibilities of left or right or biventricular heart failure, heart failure with or without fluid overload, heart failure with reduced or preserved systolic function, and a knowledge that while ischaemic heart disease is the herd, heart failure due to haemochromatosis is but one odd sheep, is not easy and something that comes with practising being a doctor, or at least a physician or aspiring physician, which should encompass most readers of this book.

Diagnosis is not always possible, or even the goal, in practising 'physicianly' medicine, and deference to uncertainty is sometimes desirable. But diagnosis is usually the key to treatment, or improving a patient's lot. And diagnosis is reliant upon knowledge of potential differential diagnoses, knowledge that rests on a firm grasp of understanding how disease arises. This is sometimes at odds with the way doctors are being trained contemporarily, with emphasis perhaps on experiential and problem-based learning, seeing cases and being taught how to treat problems encountered. It might be interesting to graze for a moment in the field of sociology (but never for very long!), and the way society has changed over the decades, reflected in all walks of life, including medicine. The post-war 'baby boom' generation (births circa 1945–65) was injected by the previous generation with a sense of duty, respect for authority and firm family values. The next generation, X (births circa 1965–85), started to explore new outlooks, with generation Y (births circa 1985–2005) taught more firmly to consider their own rights, to question received authority and wisdom and to consider work–life balance. With this have come advances in technology, globalisation, new ways of communicating and new ways of receiving information through the internet. The next generation is already experiencing a world of instant access. Society's changes have been perhaps bitter-sweet, which is reflected in medicine. There is rightly much greater emphasis on equality, work–life balance, and systems to improve safety (guidelines, protocols, assessments and e-portfolios within training, for example), and there is no doubt that patients are safer than they ever were. But we must not allow safety nets to take the edge off our thinking. And we must also ensure that training does not just ratify competence and detect doctors in difficulty, but also rewards excellence. In a 'dumbed-down' world in which it is sometimes presumed that anyone can do anything with information, we must remember that knowledge is not the same as skill or judgement and the stages from unconscious incompetence through conscious incompetence and conscious competence to unconscious competence rely on much more than knowledge. And perhaps a fifth stage, reversion to conscious incompetence, should be there in our minds as doctors, aware that the complexities of and interplay between human disease, social factors and ethical considerations are limitless. Diagnostic skills cannot be achieved from the watchful shores of e-learning, but through real life, seeing patients and developing a huge mind-map of medicine that respects the approach towards diagnosis and appreciates underlying pathophysiology, rather than assuming diagnosis and focussing on problem-solving. Dare I say it, where treatment is possible, treatment is the 'easy' bit. The real skill lies in appreciating the complexities of heart failure and its differential diagnoses, in considering whether or not the patient with asthma might be the unusual patient who in fact has eosinophilic vasculitis, and in the differentials of any other condition you encounter. We as doctors should grasp these nuances, consider the possibilities, and indeed feel duty bound to do so.

History taking probably remains about 80% of diagnosis, and examination and investigation around 10% each, but all are instrumental to its synthesis. Examination skills are waning in many parts of the world, perhaps because of greater reliance on investigation, but the downside of this double-edged sword is that 'inappropriate' or defensive investigations may often be expensively obtained as a substitute for thorough history and examination, and simply deficient 'thinking' about a problem. Good history and examination, as well as offering good defensive practice if documented appropriately, crucially and more importantly lead to more targeted investigation and more accurate diagnosis and so are more likely to help the patient. Furthermore, history and examination take us to the bedside, which inspires patient confidence far more than the emerging trend of 'virtual' ward rounds. The case of the surgeon escorting the refractory endocarditis patient back from the operating theatre after a mere 30 minutes, having cured the root cause by exposing the feet preoperatively only to discover a paronychia and decide it still within his surgical remit to perform basic surgery is not legendary, and doubtless you can think of similar examples every day. Yet examination is diminishing in the United States, with admission pressures and assumed defensive need for investigation squeezing the human doctor–patient encounter in the process. However, in the United Kingdom there is an emerging consensus that we are underestimating the legitimacy of history and examination and overestimating the value of investigation. And in the UK – believe me, despite the hurdle you may see it as – we are lucky to have PACES.

PACES tests examination skills, the ability to elicit and interpret signs, communication and the ability to take an appropriate history, awareness of differential diagnosis, clinical judgement, managing patient concerns and maintaining patient welfare. The biggest area of concern amongst examiners remains the ability of candidates to examine and elicit signs. PACES remains an asset as a threshold in the journey of an aspiring physician. The Royal College of Physicians continues to work hard in ensuring work-based assessment does not substitute for it, and to ensure that PACES remains reliable in assessment and appropriate in content and that the areas it assesses are relevant to clinical practice. For these reasons Station 5 changed a few years ago into an integrated station where bits of history and examination are brought together in more 'real-life' fashion. It is a station where the time goes rather too quickly, but this can reflect real life, too!

The aim of this book is to help you pass PACES. While candidates invariably 'just want to pass the exam', a broad grasp of relevant clinical medicine favours candidates in PACES, particularly when faced with examiners' questions. The remit of cases and examiners' questions is far reaching, and most candidates ask how to 'prepare' for PACES. This third edition, therefore, remains a textbook for PACES with explanations of why things are so, rather than a series of steps or lists to be learnt by rote. It is best used as an adjunct to core medical training. The aim is to promote deeper learning, and so more ready recall of information in the heat of' the exam. Most candidates find that time in the exam goes fast, but those who perform more strongly are those who have prepared widely, practised their examination skills thoroughly and envisaged lots of potential questions. There is certainly more rather than less information needed to pass PACES in this book, but candidates who have grasped more and practised more usually pass.

Of course you can't know everything, but more important than knowledge is initiative, and fundamental is the ability to keep thinking and asking why. For virtually any condition a patient may have, you can ask why has it occurred and why it is important in terms of consequences. This will help add detail to a diagnosis. An acute coronary syndrome may be one of the commonest hospital admission 'diagnoses', but a true physician will think about why it has happened and consider not just traditional risk factors but contemporary ones like chronic kidney disease and inflammatory disease. High cholesterol or hypertension will not be accepted as risk factors without asking if the high cholesterol could be an important familial lipid problem or if the hypertension could have a secondary cause. Acute coronary syndrome itself will not be accepted as a diagnosis without attempting to stipulate its subtype and its location through the examination of electrocardiograms. Potential consequences such as heart failure or conduction block also help paint detail onto a sketch diagnosis, most importantly with consideration of what the patient is experiencing.

Developing wide differential diagnoses to work from and creating detailed diagnoses through asking why are fundamental to being a clinician – and fundamental to getting through exams.

A lot has been said here about diagnosis. Of course when it comes to managing a patient, through investigation or treatment, the right answers come only by engaging with that patient or, if he or she lacks capacity, family or others close to the patient or involved in his or her care.

A number of new features have been introduced into this third edition. The most obvious is the updated section for preparation for Station 5. Elsewhere all text has been entirely updated and some new illustrations incorporated.

My editor, Pauline Graham, and the team at Elsevier have continued in the remarkable job of producing a book that is very easy to navigate. The ease of orientation makes it a lot easier for you to skip through areas where you feel confident, and linger in areas where you feel lost. The book should continue to appeal to aspiring medical students seeking a case-based textbook of medicine.

Do not forget that, despite all of the pressures and pulls of practising medicine, the doctor–patient relationship remains central to what we do, and diagnosing or appreciating the problems presented to us is central to the goal of improving the patient's situation. It is central to our training, and central to the existence of the environments in which we work. Your job in preparing for your exam is also to see patients. This book is a map. The adventure is yours.

Good luck.
Tim Hall

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Introduction

THE PRACTICAL ASSESSMENT OF CLINICAL EXAMINATION SKILLS (PACES)

PACES comprises a series of timed assessment stations where various competencies are tested by examiners with an objective marking scheme. Its main strength is in minimising bias, and it has been shown to have validity, reliability and relative practicality. PACES was introduced in 2001 and the basic format has been highly successful. But in October 2009 significant changes were made to the examination worldwide, the main ones being the name, content and structure of Station 5 and the marking system. The overall standard of the examination remains the same.

Structure

The PACES examination consists of five clinical stations, each assessed by two independent examiners. Candidates will start at any one of the five stations, and then move round the carousel of stations, at 20-minute intervals (Fig. 1), until they have completed the cycle. There is a 5-minute period between each station, giving a total time of 125 minutes.

The start and finish of each station is signalled by a bell, although it is the duty of examiners to indicate the passing of time during each station. A different pair of examiners is at each station. One examiner takes the lead in conducting the examination with the first candidate, the other examiner conducts the next, and so on. There is a 5-minute seated interval between stations.

Stations 1 and 3: the clinical examination stations

At Stations 1 and 3 (each of which consists of two sub-stations lasting 10 minutes), the timekeeper sounds a bell to announce the start of the assessment at the station. One examiner takes the candidate into the station and shows the candidate written instructions for the first of the two cases. The candidate responds to the written instructions. The response involves the examination of the appropriate system and answering questions from the examiners that may include the diagnosis and management of the clinical problem. After 5 minutes, the examiners will remind candidates that there is 1 minute remaining in which to complete their physical examination (i.e. a total of 6 minutes is permitted). After 6 minutes, the physical examination will end, leaving 4 minutes for discussion of the case. After 10 minutes, the timekeeper signals the end of the sub-station. The examiners and the candidate must then stop. The candidate is then shown written instructions by the second examiner for the second case. Examination at the second sub-station then starts and follows the same procedure as the first sub-station. After 10 minutes, a bell sounds to signal the end of the examination at the station. The examiners and the candidate must then stop. The candidate leaves the station and is directed to the next station. A period of approximately 5 minutes has been allowed for this changeover and for the examiners to complete the marksheets.

Stations 2 and 4: history-taking skills and communication skills and ethics

Stations 2 and 4 each last 20 minutes. At Station 2, the candidate is given a general practitioner's letter to read outside the station in the 5-minute period before the start of the station. At Station 4, the candidate is given a clinical scenario to read. Rough paper is provided for note taking (these notes do not form part of the examination and are destroyed afterwards). The timekeeper sounds a bell to announce the start of the station. One examiner takes the candidate into the station. The interview involves interaction between the candidate and the patient subject appropriate to the station. Candidates are alerted when 12 minutes and again when 14 minutes have elapsed. The

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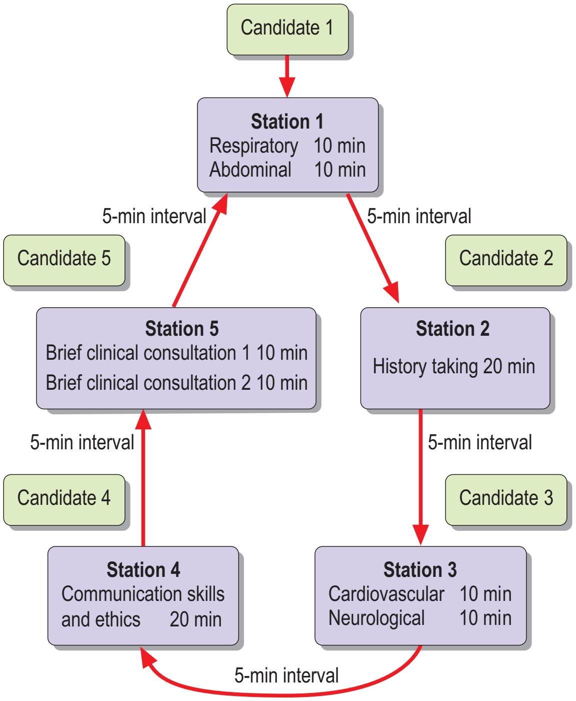

Figure 1 PACES carousel.

simulated patient leaves the station after 14 minutes. The candidate is given 1 minute for reflection, or to make further notes, and is then invited to summarise and discuss important features of the history (Station 2) or the interaction with the simulated patient (Station 4). At Station 2 the examiners will ask about the implications of problems identified and strategies for management. At Station 4 the examiners are encouraged to identify ethical implications and discuss issues arising from the interview.

Documents for Station 2

The documents include candidate, patient and examiner information sheets. The format of these information sheets is reflected in the format of the cases in Station 2 of this textbook, the template for which is outlined later in this chapter. Below is an outline of the information that candidates and patients receive and the information that examiners receive and expect.

Candidate information includes:

- The name and age of the patient.
- The *role of the candidate* (e.g. you are a doctor in the medical outpatient clinic or on the ward).
- The presenting complaint.
- The following *advice on timing*: 'Please read the letter printed below. When the bell sounds, enter the room. You have 14 minutes to take a history from the patient, 1 minute to collect your thoughts and 5 minutes for discussion. You may make notes if you wish.'
- The *scenario*, usually a referral letter from the patient's GP. This should be addressed to the doctor in the outpatient department or admissions unit and not to a location requiring specialist knowledge such as a neurology clinic. It should pose a question (e.g. asking for advice on diagnosis, investigation, drug therapy, complications or specialist referral) so that a task is posed for the candidate. It should be brief, not providing all of the history but sufficient information to sustain a 14-minute interview. Aspects of the social, family and past medical history may be mentioned to allow candidates to explore these in more detail. Relevant examination findings and values of investigations (with normal ranges for less common investigations) may be given. The topic should not be esoteric or obscure and the candidate should be expected to have some knowledge of it. The candidate is invited to make notes on paper provided. The description of patients by their diagnoses should be avoided ('diabetic', 'epileptic') in favour of 'patients with (diabetes, epilepsy)'. Abbreviations are avoided wherever possible except universally accepted abbreviations such as ECG and CXR. Trade names of drugs should be avoided. The station should be seen as an exercise in information gathering to reach a differential diagnosis. The content and instruction should not divert the candidate to predominantly engage in a communication skills exercise.
- The *candidate's task*, i.e. to interview the patient and, based on the history obtained, construct a differential diagnosis and plan. This should be explained to the patient and any questions they may have answered.
- A reminder that the candidate is not required to examine the patient.

Patient (surrogates are used) information includes the role and location of the patient and a scenario. The scenario includes presenting symptoms, past medical history, medication history, personal history, concerns, expectations and wishes, and questions they might ask. Patients are requested not to withhold information, but not to volunteer information that has not been appropriately sought.

Examiner information includes a summary of candidates and patient information, together with a reminder to advise candidates when there are 2 minutes remaining (i.e. after 12 minutes). Examiners are reminded that a good candidate would be expected to take a history, which includes a detailed social history and activities of daily living, and to focus particularly on the questions raised in the referral letter. Further, that at the end of the consultation the candidate should have discussed solutions to the problems posed by the case and also given the patient opportunity to ask any further questions before closure. It is not necessary for candidates to agree a summary with the patient during their interview.

Documents for Station 4

These include candidate, patient and examiner information sheets. The format of these information sheets is reflected in the format of the cases in Station 4 of this textbook, the template for which is outlined later in this chapter. Below is an outline of the information candidates and patients receive and the information examiners receive and expect.

Candidate information includes:

- The *role of the candidate* (e.g. you are a doctor in the medical outpatient clinic on the ward).
- A brief definition of the *problem* (e.g. breaking bad news).
- The name and age of the patient.
- The following *advice:* 'Please read the scenario printed below. When the bell sounds, enter the room. You have 14 minutes for your consultation with the patient, 1 minute to collect your thoughts and 5 minutes for discussion.'
- The *scenario*. The scenario should reflect everyday clinical practice and not be too obscure or complex. It should not rely on detailed knowledge of one condition, investigation, current management or prognosis. It should be sufficiently detailed to sustain a 14-minute discussion and as comprehensible as possible such that the candidate does not engage primarily in a history-taking exercise but has enough information to communicate. It should have an ethical component because it may be difficult for examiners to sustain a discussion based solely on communication skills. The topic should be a universal problem applicable to global medicine and must not require detailed knowledge of UK law. The scenario should clearly define the *task* for the candidate.
- A reminder that the candidate is not required to take a history or to examine the patient.

Patient (surrogates are used) information includes the *name and age* and role of the patient, a summary of the problem and a scenario. The scenario includes a description of the attitudes and emotional responses, and a list of concerns or possible questions.

Examiner information includes a summary of candidates and patient information, together with a reminder to advise candidates when there are 2 minutes remaining (i.e. after 12 minutes). Examiners are reminded that a good candidate would be expected to have agreed a summary plan of action with the subject before closure. Nevertheless, in discussion, the examiners will usually ask the candidate (after 1 minute's reflection) to summarise the problems raised in the foregoing exchange. Candidates should be asked to identify the ethical and/or legal issues raised in this case and how they would address them.

Station 5: integrated clinical assessment

The integrated clinical assessment assesses the way in which candidates approach a clinical problem in an integrated manner, using history taking, examination, and communication with a patient or a surrogate patient. It reflects the way in which clinical problems are considered in the ward, emergency medical admissions unit or medical outpatient clinic in normal clinical practice. There are two cases, each lasting 10 minutes and known as a 'brief clinical consultation'. The patient has a short narrative giving the agreed history detailing his or her complaints and the information he or she would like from the candidate's consultation with him or her.

The way in which candidates approach this station is very different from the formal examination of systems at Stations 1 and 3, and from the structured and comprehensive history-taking and communication exercise at Stations 2 and 4. Candidates aim to elicit sufficient history to make an assessment of the problem presented and carry out an examination that is relevant to assessing the problem presented. The history taking and the examination are not intended to be comprehensive – these are not 'long cases' or full outpatient consultations. Candidates have 8 minutes to take a focused history, carry out a relevant examination and respond to the patient's concerns. During the remaining 2 minutes, an examiner will ask the candidate to describe the positive physical findings and to give a preferred diagnosis and any differential diagnosis. Candidates will always be given the full 8 minutes with each of their patients and the examiners will not begin their 2-minute discussion until the 8 minutes have elapsed.

It is not necessary, nor would it be possible, for candidates to undertake a complete history or comprehensive examination. The aim of the encounters is to allow candidates to show that they can focus on the most important parts of history and examination when posed with a clinical problem. In addition, candidates will be expected to explain their management plan succinctly to patients and answer any questions they might have.

Candidates may examine the patient and take aspects of the history in any order, or concurrently. For example, where the patient complains of a physical abnormality, the candidate may wish to examine affected areas while asking the patient about relevant history. The cases presented to candidates will all offer a clinical problem relevant to general or acute medicine that can be addressed in an 8-minute consultation. They may be skin, locomotor, endocrine or eye problems as found in the former Station 5, but the cases would be presented as clinical problems that can be assessed from history and examination, and with the requirement to respond to the patient's concerns. The cases may also comprise clinical problems encountered in routine hospital medical practice and contained in the Curriculum for General and Acute Medicine, available on the Joint Royal Colleges of Physicians Training Board (JRCPTB) website. Examination of the optic fundus is still required in some encounters. Patients with problems relating to disciplines or areas less commonly represented in the former examination, for example acute medicine, haematology, infectious disease and elderly medicine, may now also be encountered.

Skin, locomotor, eyes and endocrine problems are well suited to the new style of Station 5, presented as clinical problems rather than spot diagnoses. However, these four disciplines will not now always be represented in the examination, although clinical problems relating to those disciplines will frequently appear at Stations 2, 4 or 5, so candidates must continue to be prepared to assess patients whose problems primarily relate to these systems.

Documents for Station 5

These include candidate, patient and examiner information sheets. The format of these information sheets is reflected in the format of the cases in Station 5 of this textbook, the template for which is outlined later in this chapter. Below is an outline of the information candidates and patients receive and the information examiners receive and expect.

Candidate information includes:

- *Advice* that the candidate has 10 minutes with each scenario and that the examiners will alert the candidate when 6 minutes have elapsed, stop the candidate at 8 minutes, and that in the remaining 2 minutes one examiner will ask the candidate to report abnormal physical signs (if any), the diagnosis or differential diagnosis, and a plan for management (if not already clear from your discussion with the patient).
- The *role of the candidate* (e.g. you are the medical doctor on call).
- The name and age of the patient.
- A brief (often one sentence) *scenario* (e.g. This 38-year-old lady complains of pain in her left calf and she feels it may be swollen).
- The *task* (i.e. to assess the patient's problems and address any questions or concerns raised by the patient by means of a relevant clinical history and a relevant physical examination) and a reminder that history need not be completed before carrying out appropriate examination.
- A reminder that the candidate should respond to any questions the patient may have, and advise the patient of the probable diagnosis (or differential diagnoses) and the plan for investigation and treatment where appropriate.

Patient (surrogates are used) information includes questions or concerns the patient has.

Examiner information includes a summary of candidates and patient information, together with a reminder to advise candidates when there are 2 minutes remaining (i.e. after 6 minutes). Examiners are reminded to ask the candidate to describe any abnormal physical findings and to give the preferred diagnosis and any differential diagnosis, and advised that remaining areas of uncertainty (e.g. regarding the plan for investigation or management of the problem) may be addressed in any time that remains.

Marking system

Sixteen marksheets in total are completed by the examiners: one by each examiner at Stations 2 and 4 (total 4) and two by each examiner at Stations 1, 3 and 5 (total 12). The marks awarded on all 16 marksheets determine the candidate's overall score. Candidates are awarded marks for between four and seven separate clinical skills at each patient encounter (Tables 1 and 2), allowing a minimum of eight and a maximum of 16 judgements to be made on each candidate's performance in each skill over the course of the examination. All marks are recorded on a three-point grading system. The grades are 'unsatisfactory', 'borderline' and 'satisfactory'. These grades are converted to numeric values 0–2 (unsatisfactory = 0, borderline = 1, satisfactory = 2). Grade descriptors are provided on the

Table 1 Seven clinical skills in the PACES examination

	Clinical skill	Skill descriptor
A	Physical examination	Demonstrate correct, thorough, systematic (or focused in Station 5 encounters), appropriate, fluent, and professional technique of physical examination.
B	Identifying physical signs	Identify physical signs correctly, and not find physical signs that are not present.
C	Clinical communication	Elicit a clinical history relevant to the patient's complaints, in a systematic, thorough (or focused in Station 5 encounters), fluent and professional manner.
D	Differential diagnosis	Create a sensible differential diagnosis for a patient that the candidate has personally clinically assessed.
E	Clinical judgement	Select or negotiate a sensible and appropriate management plan for a patient, relative or clinical situation. Select appropriate investigations or treatments for a patient that the candidate has personally clinically assessed. Apply clinical knowledge, including knowledge of law and ethics, to the case.
F	Managing patients' concerns	Seek, detect, acknowledge and address patients' or relatives' concerns. Listen to a patient or relative, confirm their understanding of the matter under discussion and demonstrate empathy.
G	Maintaining patient welfare	Treat a patient or relative respectfully and sensitively and in a manner that ensures their comfort, safety and dignity.

Table 2 Combinations of skills assessed at each encounter

Station	Encounter	Skills assessed
1	Respiratory	A, B, D, E, G
1	Abdomen	A, B, D, E, G
2	History	C, D, E, F, G
3	Cardiovascular	A, B, D, E, G
3	Nervous system	A, B, D, E, G
4	Communication	C, E, F, G
5	Brief clinical consultation 1	All seven
5	Brief clinical consultation 2	All seven

Box 1 **Interpretation**

You will not have time to examine for all the features given under the 'Interpretation' headings in this book. Many of the features can merely be reported to examiners as those you would look for in practice. Most important is having a framework to guide you through examining and presenting.

It may seem artificial to separate signs under the headings 'Recognition' and 'Interpretation'. For example, you may have recognised aortic stenosis and during your initial examination elicited signs of severity. The 'Interpretation' section serves merely to organise these signs in a checklist, which aids thought gathering and subsequent presentation.

Furthermore, 'Interpretation' in this book does not always mean actively examining. Time may be more wisely spent sharing your knowledge under the headings listed than examining.

marksheets and are further refined in the examiner calibration process that takes place before each candidate is seen. PACES is marked out of a total of 172 marks (the maximum available from the 16 marksheets).

PACES FOR THE MRCP

Stations 1 and 3: the clinical examination stations

The clinical examination cases should reflect everyday clinical medicine, with less emphasis these days on esoteric conditions. However, an *important difference between these cases and real practice is that these cases bypass history taking and focus on clinical examination*:

- The ability to *examine* systems
- The ability to *recognise* signs
- The ability to *interpret* those signs
- The ability to *discuss* matters arising from the case.

To help you prepare for these stations the cases in *PACES for the MRCP* follow a consistent approach. This approach is designed to structure your knowledge and sharpen your clinical skills to directly meet the needs of the PACES examination. The approach can also be used on the wards in preparation for PACES so that you are 'primed' for using it in the examination.

Instruction

An example of the type of written instruction for candidates is given for each case within each system.

Individual cases follow the Recognition–Interpretation–Discussion (RID) format, as follows.

Recognition

You are accustomed in practice to converging upon diagnoses through history taking, examination and investigations. In PACES, examination skills are paramount in eliciting diagnoses and patients tend to have diagnoses that are readily disclosed by examination. This is not always so in practice, and in some ways PACES requires the reverse of your approach in practice.

The first thing to do is work out what it is that you are being asked to look at. This book describes (in a form which can be easily recited to the examiners) the *clinical signs* that help you to decide this.

You will be looking at one of two broad abnormalities:

1. *A specific diagnosis* (e.g. rheumatoid arthritis)
2. *A pattern of signs for which there may be numerous differential diagnoses* (e.g. lung consolidation, chronic liver disease, Horner's syndrome, spastic paraparesis).

Interpretation

Recognising the abnormality is your first goal. To comfortably pass you must then attempt to further interpret your initial findings. You should *know what to do next before presenting your initial findings* and *decide how you are going to present all of your findings* to the examiners.

The important extra information to gather next and a framework for presenting it all (Box 1) is organised within one or more of four subheadings.

Confirm the diagnosis

This is important, especially if there is *diagnostic ambiguity*. For example, a systolic murmur is more likely be aortic stenosis if it is ejection in nature, present at the upper right sternal edge and louder sitting forward and in expiration.

What to do next – consider causes or assess other systems

Considering causes may be important in cases in which you have recognised a *pattern of signs for which there could be numerous differential diagnoses*. An example is to look for or tell your examiners that you would look for signs of a Pancoast's tumour if you find Horner's syndrome.

Assessing other systems may be important in cases where you have recognised a *specific diagnosis*. For example, if you diagnose Crohn's disease on the basis of erythema nodosum in a patient you are told has bowel symptoms then it is important to consider the extraintestinal manifestations of inflammatory bowel disease. There would not be time to examine for all of them, but this book outlines those your examiners would expect you to know. You might look briefly for one or two and mention some others.

Consider severity/decompensation complications

In many cases it is important to determine whether there are signs associated with increased morbidity and mortality. An example is aortic stenosis, for which there are established signs indicating severe disease.

It may be important to look specifically for signs of decompensation, such as signs of hepatocellular failure in chronic liver disease.

Consider function

Awareness of the possible effects of a diagnosis on your patient's functional status is very important. For example, a patient with rheumatoid arthritis may have marked difficulty with grip and a patient with chronic lung disease may be housebound.

Discussion

The key to impressing examiners is in ever striving 'to go further'. Examiners prefer candidates who spontaneously present their findings and thoughts. Examiners are less certain of candidates from whom information has to be 'dragged'.

From an examiner's perspective you do two things in each case. Firstly, you *examine* your patient. Secondly, you *present* your findings. From your perspective you are doing a lot more. While examining you are looking for signs, deciding how to further interpret your findings and thinking about how you might present them. The recognition and interpretation framework in this book should aid both your examination of patients and your presentation to examiners. By adopting this framework of *diverging* from your initially recognised findings and reporting more information to the examiners spontaneously, you will perform well. The examiners can interrupt at any point with questions but are less likely to do so early if you appear to have a structured approach. At some stage, however, examiners will ask you questions, and your presentation will merge into a discussion.

The discussion sections of each case in this book provide, through questions and answers, revision of important areas of 'MRCP medicine' you might be expected to discuss. You are expected to have a working knowledge of the causes, underlying pathophysiology, symptoms, investigation and further management of the wide range of conditions that you could encounter in PACES.

Questions and answers tend to be a more effective way of learning information than straight text. It is very easy to skim through pages of text thinking 'I know this' without really knowing it at all! Questions, on the other hand, make you think. The answers given in this book are sometimes quite long, often covering more than the examiners would expect (especially in the short time available) but have been designed to maximise your understanding of each disease. Remember that the emphasis in PACES is on common conditions, and that you even know which system you are being examined on. Recognising common conditions may not be especially discriminating. Rather, the examiners will be testing your wider knowledge about these common conditions.

Station 2: history-taking skills

The introduction in Station 2 gives details on developing history-taking skills. The template used for the 50 cases described for this station is given below. Note that in PACES there are sheets of instructions and advice for the candidate, the patient and the examiners providing detailed information similar to that described earlier in this chapter, although the exact organisation and wording on the sheets tends to change in subtle ways over time. Thus the candidate and patient information sections here are abridged rather than repeating those long and detailed instructions 50 times. The emphasis herein is correctly on the approach you should take that will ensure structure and effectiveness and impress the examiners.

Candidate information

Role

You are a doctor in the medical outpatient clinicon the acute medical unit (or the medical ward or specialty ward, e.g. an elderly care ward, the stroke unit) about to see the patient below. Please read the letter from this patient's GP. You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Dear Doctor

Re: Mr/Mrs/Ms …aged…
    Details of case

Yours sincerely

Scenario

Please take a history from the patient (if you wish you may continue to make notes on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Details are given about the patient (actually a surrogate) – herein in third person.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

There follows a list of areas to cover in the interview, under the following headings:

- Presenting problems and symptom exploration
- Patient perspective
- Past medical history
- Drug and allergy history
- Family history
- Social history.

These are followed by a summary box.

SUMMARY BOX – ASSESSMENT AND PLAN

Your task in all 50 cases is essentially to interview the patient and, based on the history, construct a differential diagnosis and plan. This should be explained to the patient and any questions they may have answered. Although you are not required to close the interview with a summary, most candidates find that it is natural to do so, covering the assessment and plan, ideally at the 12-minute point. This helps organise thoughts, facilitate questions from the patient and act as a springboard for inviting questions from the examiners. The summary boxes herein cover initial differential diagnoses, investigations and treatments.

Discussion

A series of questions and answers relating to the case are designed to improve your knowledge of the topic and equip you to answer the examiners' questions.

Station 4: communication skills and ethics

The introduction in Station 4 gives details on developing communication skills and understanding the principles of medical ethics. The template used for the 50 cases described for this station is given below. Note that in PACES there are sheets of instructions and advice for the candidate, the patient and the examiners providing detailed information similar to that described earlier in this chapter, although the exact organisation and wording on the sheets tends to change in subtle ways over time. Thus the candidate and patient information sections here are abridged rather than repeating those long and detailed instructions 50 times. The emphasis herein is correctly on the approach you should take that will ensure structure and effectiveness and impress the examiners.

Candidate information

Role

You are a doctor in the medical outpatient clinicon the acute medical unit (or the medical ward or specialty ward, e.g. an elderly care ward, the stroke unit). Please read this summary.

Scenario

Re: Mr/Mrs/Ms … aged …
Details of the problem(s) to be discussed

Your task(s) is/are to …

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Details are given about the patient/subject (actually a surrogate) – herein in third person.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

There follows a list of 10 points to cover in the interview.

Discussion

A series of questions and answers relating to the case are designed to improve your knowledge of the topic and equip you to answer the examiners' questions.

Station 5: integrated clinical assessment

The template used for the 50 cases described for this station is given below. Note that in PACES there are sheets of instructions and advice for the candidate, the patient and the examiners providing detailed information similar to that described earlier in this chapter, although the exact organisation and wording on sheets tends to change in subtle ways over time. Thus the candidate and patient information sections here are 'vignettes' rather than repetition of those long and detailed instructions 50 times. The emphasis herein is on the approach you should take that will ensure structure and effectiveness in your handling of whatever case you encounter.

Candidate information

Role

You are a doctor in the medical outpatient clinicon the acute medical unit (or the medical ward or specialty ward, e.g. an elderly care ward, the stroke unit).

Scenario

Re: Mr/Mrs/Ms … aged …

Patient problem or concern (e.g. this 38-year-old lady complains of pain in her left calf and she feels it may be swollen).

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

Details are given about the patient.

Focused history and examination

The focused history and examination do not necessarily have to be done in a specific order, and should be seen as an opportunity for integrated assessment as seen on a post-take ward round. The purpose is to push the boundaries away from basic knowledge and technique towards the higher skills of professionalism and expertise. This is reflected in the fact that although the station constitutes one-fifth of the examination it accounts for almost one-third of the total marks since all seven clinical skills are assessed.

Initial history

Generally open questions should be used to develop closed questions.

Initial examination

This should look for obvious signs that may prompt a diagnosis or initial differential diagnosis, similar to the 'Recognition' section used in Stations 1 and 3.

Further assessment

This might include, through further history or examination, assessment of other systems or assessment for possible causes, and sometimes an assessment for complications. Patient concerns should also be explored.

Feedback to patient

This is organised as a spiel that the candidate would say in 1 minute:

- Explaining the diagnosis or differential diagnosis
- Explaining the initial plans for further investigation and management
- Addressing the patient's concerns
- Checking that the patient understands the information and asking whether there are any questions. The techniques of checking and repetition, and avoiding jargon, are important.

Feedback to examiners

This is organised under the following three headings, again written as a spiel that the candidate would say, this time to the examiners:

- Summarise the key history and examination findings
- Provide a diagnosis or differential diagnosis with supporting evidence
- Outline an investigation and management plan.

FURTHER READING

- Royal College of Physicians (London) www.rcplondon.ac.uk.
- Royal College of Physicians (Edinburgh) www.rcpe.ac.uk.
- www.mrcpuk.org.

Station | 1 |

Respiratory and abdominal system

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Respiratory system

Examination of the respiratory system

Inspection

General

- Introduce yourself, ensure that the patient is sitting comfortably at 45° and then stand back. Placing your hands behind your back is a good way to show you remember the importance of inspection.
- Look around the bedside for metered dose inhalers, nebulisers or sputum pots.
- Note any cachexia.
- Count the respiratory rate (tachypnoea, defined as a respiratory rate > 20 breaths /minute (normal is 12–20 breaths/minute, albeit arbitrary), is often the first sign of respiratory or haemodynamic compromise) and note if the patient is breathless at rest.

Listen

- Listen to the breathing with unaided ears, noting any of the sounds listed in Box 1.1.

Hands

- Look for tar staining, clubbing, peripheral cyanosis or wasting. Clubbing very rarely progresses to hypertophic pulmonary osteoarthropathy, characterised by swelling and tenderness around the wrists and ankles associated with toe clubbing.
- Feel the pulse whilst inspecting the hands to determine if it is bounding; note any flapping/tremor.

Face

- Look for central cyanosis (best seen at the tongue).
- Look for pursed lip breathing.
- Note any Horner's syndrome.

Box 1.1 **Sounds in respiratory disease you might hear before auscultation**

- Expiration longer than inspiration (obstructive airways disease)
- Expiratory wheeze (obstructive airways disease)
- Inspiratory stridor (obstruction of upper airways, e.g. mediastinal mass, bronchial carcinoma)
- Clicks (bronchiectasis)
- Gurgling (airway secretions)

Neck

- Look at the jugular venous pulse (JVP). The JVP is raised and pulsatile in cor pulmonale but fixed in superior vena cava obstruction, the latter characteristically causing marked venous distension in the neck and sometimes distension of veins in the hands, the underside of the tongue and upper chest wall.
- Note any phrenic nerve crush scars in the supraclavicular fossae.

Chest

- Look at the size and shape (Box 1.2) of the chest, and note any deformities (e.g. kyphoscoliosis, pectus carinatum, pectus excavatum), thoracotomy scars, radiotherapy field markings, telangiectasia or muscle wasting.
- Look at chest wall movement (upwards in emphysema; asymmetrical in fibrosis, collapse, pleural effusion or pneumothorax).
- Note any use of accessory muscles, including abdominal or scalene muscles, or intercostal indrawing.

Palpation

Neck

- Feel the trachea to determine any mediastinal shift (using the middle finger as the exploring finger and the index and ring fingers resting on the manubriosternum either side; Fig. 1.1) and note the approximate cricoid–suprasternal notch distance, decreased in hyperinflation from the normal three finger-breadths.
- Feel for cervical, supraclavicular and axillary lymph nodes, always from behind using flat fingers and not poking with fingertips.

Chest

- Start at the front or back (you are more likely to find signs at the back) but complete all of front or back examination before moving to the other. Remember that the lower lobes occupy most of the posterior chest and the upper lobes the anterior chest (Fig. 1.2).

Box 1.2 **Big or small chest?**

As a simple rule, a 'big chest' (with a large anteroposterior diameter, little lateral expansion, and lifting of the rib-cage on inspiration) alerts you to chronic obstructive pulmonary disease, whilst a 'small chest' alerts you to possible fibrotic lung disease.

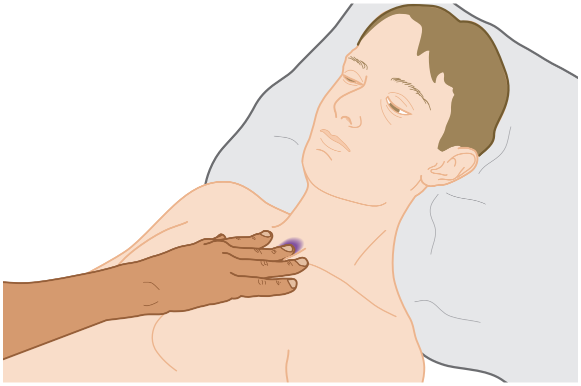


Figure 1.1 Determining the position of the trachea.

- Examine chest expansion. For the inframammary area and for the back of the chest use a 'bucket handle' approach with your fingers in the intercostal spaces either side of the chest and your thumbs floating in the midline (Fig. 1.3). This allows the ribs to move outwards. For the supramammary area, where the ribs move predominantly upwards, place your hands on the chest wall with thumbs meeting.
- Tactile vocal fremitus gives the same information as vocal resonance and may be omitted.

Percussion

Percussion sites

- Percuss the supraclavicular areas, clavicles and chest on both sides (Fig. 1.4). More than four or five levels of percussion is time consuming as a screen but percuss further to delineate any abnormality you find.

Percussion technique

- Compare right with left and superior with inferior (left → right at same level → right inferiorly → left at same level → left inferiorly → right at same level and so on).
- Ensure that the finger applied to the chest (left middle) is applied firmly, and aligning it with the ribs is preferable; the pad of the partly flexed percussing finger (right middle) should tap the middle phalanx of the chest finger lightly, springing away quickly after contact to avoid dampening of the note. This relaxed swinging motion should come from the wrist, not the forearm (Fig. 1.4 inset).
- Remember that the upper level of liver dullness is around the sixth rib in the right mid-clavicular line. Resonance below this level is a sign of hyperinflation. Cardiac dullness may also be elicited.

Auscultation

Auscultation is traditionally with the diaphragm, but the bell may not provoke as much extraneous sound from hairy chests and is able to get into the supraclavicular areas. The patient should breathe comfortably with the mouth open.

- Auscultate, as for percussion, the supraclavicular areas, axillae and upper, middle and lower chest for breath sounds, added sounds and vocal resonance.

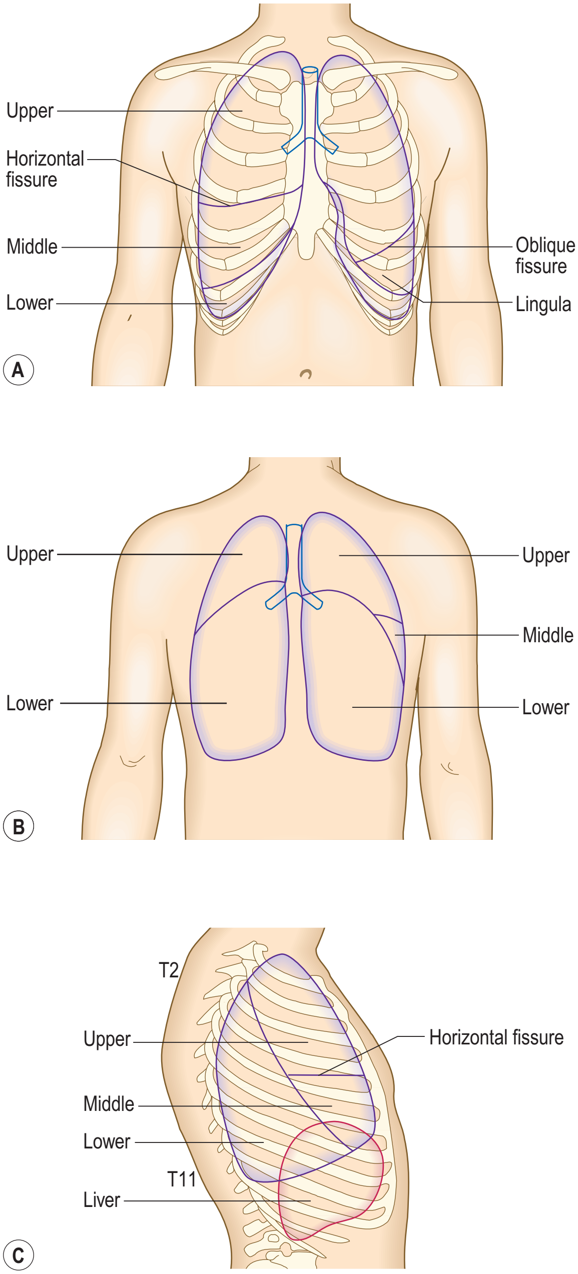


Figure 1.2 Surface markings of the lobes of the lungs: (A) anterior, (B) posterior, (C) lateral view. *(From Douglas, G., Nicol, F., Robertson, C., 2009 Macleod's Clinical Examination, Twelveth ed. with permission.)*

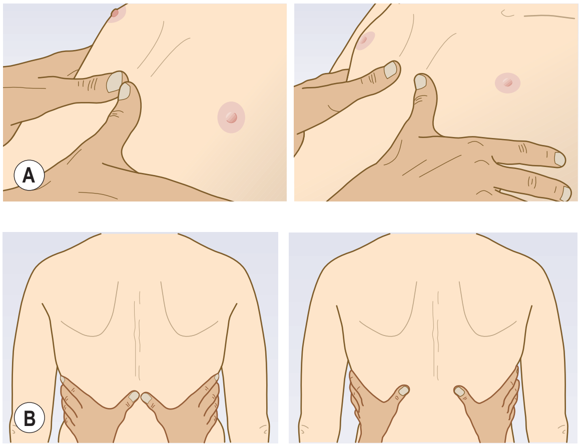


Figure 1.3 Assessing chest expansion: (A) anterior, (B) posterior. *(From Douglas G., Nicol F., Robertson C., 2009. Macleod's Clinical Examination, Twelveth ed. with permission.)*

Breath sounds and added sounds

These are described in Table 1.1.

Vocal resonance

- Vocal resonance, like tactile vocal fremitus, represents transmission of sound from the central airways to the chest wall. Sound transmission is enhanced through solid tissue (consolidation) provided the airways are patent and attenuated through fluid (pleural effusion) compared with transmission through air (normal). The principles are as for bronchial breathing in consolidation and reduced breath sounds in a pleural effusion. Enhanced sound transmission in consolidation is analogous to the vibration of an earthquake that can be felt through the ground before it can be heard through the air. Attenuated sound in a pleural effusion is analogous to diving underwater, the sound of people on land suddenly muffled. 'Ninety-nine' is the conventional sound used to assess vocal resonance, but the intended nasal 'oi' is better demonstrated by 'neun-und-neuzig'.
- Whispering pectoriloquy, when whispered sounds are heard clearly, confirms consolidation because a whispered voice is clearly audible through solid lung. Aegophony is an unusual sign in which compressed lung above a pleural effusion creates a high-pitched bleat from conducted voice.

Additional ward tests

- Mention that you would perform ward spirometry and pulse oximetry as part of your examination.

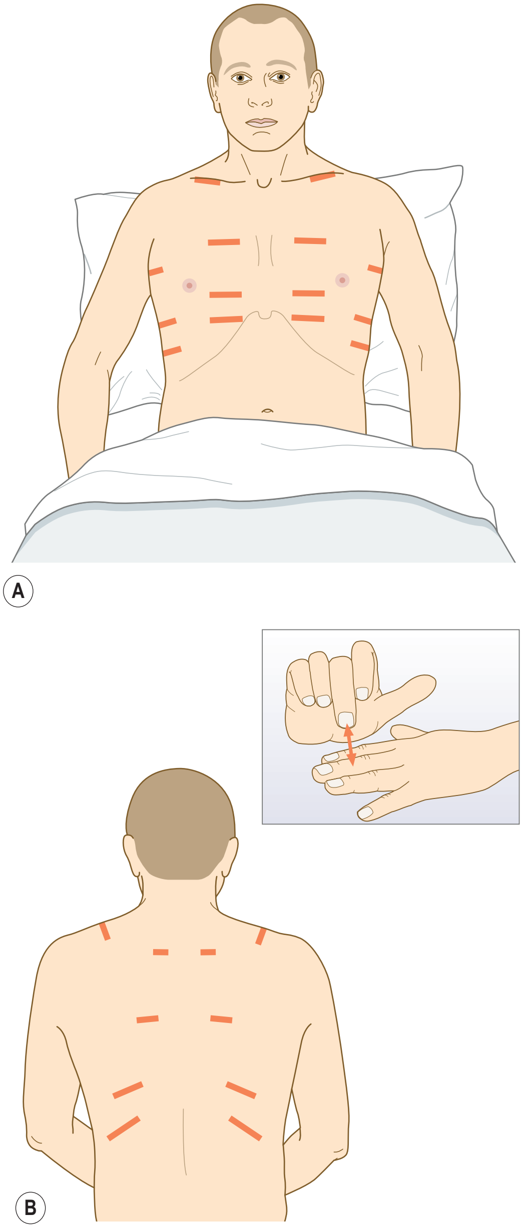


Figure 1.4 Percussion sites and technique: (A) anterior, (B) posterior. *(From Douglas, G., Nicol, F., Robertson, C., 2009 Macleod's Clinical Examination, Twelveth ed. with permission.)*

Integration

Some patterns of important focal abnormalities are shown in Figure 1.5.

Summary

A summary of the respiratory system examination sequence is given in the Summary box.

Table 1.1 Breath sounds and added sounds

Sounds			What they represent		What they sound like	When they are heard
Breath sounds	Quality	Normal (vesicular) breath sounds	Air turbulence in large airways filtering through lung substance to chest wall		Louder and longer in inspiration than expiration No gap between inspiratory and expiratory sounds	Normally
		Bronchial breath sounds	Air turbulence in large airways not filtered by alveoli, producing a different quality They occur in any situation where normal lung is replaced by uniformly conducting tissue, since solid lung conducts unfiltered sound to chest wall Note: Amphoric breath sounds occur over a large cavity and have exaggerated bronchial breathing quality, with lower pitch but higher resonance (likened to air passing over the top of a hollow jar)		Hollow, blowing Heard throughout expiration Inspiration and expiration more equal in duration Pause between inspiration and expiration Resemble sound when stethoscope applied to neck (but quieter)	Over an area of consolidation (very rarely over localised fibrosis, collapse or just above a pleural effusion), i.e. in any situation where normal lung is replaced by uniformly conducting tissue, since solid lung conducts unfiltered sound to chest wall
	Intensity (it is preferable to describe breath sounds as normal or reduced in intensity, and not the term 'air entry' which cannot be directly determined from breath sounds)	Normal	Breath sounds are produced in airways and not alveoli (vesicles) as once thought; intensity varies with voluntary effort		Loud or quiet depending on effort	Normally
		Reduced	Filtered sound		Quiet	Consolidation Collapse Pleural effusion Hyperinflation Pneumothorax
Added sounds	Crackles	Early and mid-inspiratory		Sounds come from larger airways and so are similar in different areas of lung	Tend to be coarse If clear or change on coughing and occur in expiration are likely to be due to airway secretions	Pneumonia Bronchiectasis
		Late inspiratory		Sounds come from smaller airways and depend on gravitational forces and so can vary over small areas	Tend to be fine Best heard at lung bases where small airways close on expiration Pulmonary fibrosis sounds like 'Velcro' (in early disease basal posterior crackles that are reduced leaning forward); positional changes occur slowly in pulmonary oedema	Pulmonary fibrosis Pulmonary oedema (occasionally coarse)
	Wheeze (continuous sound)	Polyphonic expiratory	Flow through narrowed airways Pitch depends more on flow rate than airway calibre Usually expiratory, since airways dilate on inspiration, inspiratory wheeze tending to indicate severe obstruction	Diffuse narrowing of airways	Expiratory Polyphonic	Chronic obstructive pulmonary disease Asthma
		Monophonic		Narrowing of single large airway	If fixed obstruction similar in inspiration and expiration When large airway narrowing subject to pressure change, site of narrowing determines pattern; stridor is a loud monophonic wheeze prominent on inspiration (extrathoracic narrowing)	Laryngeal obstruction Tumour
		Biphasic noise		Often obstruction above the larynx – stertorous breathing	Inspiratory and expiratory noise	Tracheal obstruction Severe tonsillitis
	Pleural rub		Superficial scratching or grating sound on deep inspiration (like the crackle of leaves underfoot on an autumn forest floor, or the crunching underfoot of freshly fallen snow) Note: A pericardial crunch is a rare sound synchronous with the heartbeat in a pneumomediastinum or small left-sided pneumothorax		Sounds 'close' to the stethoscope Does not change with coughing Can vary with time and position	Pulmonary embolism Pneumonia

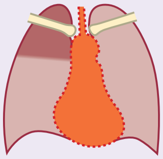
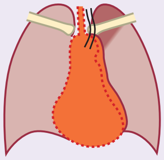
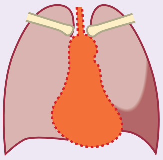
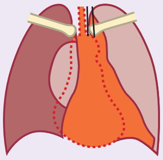
		Tracheal deviation (mediastinal shift)	Chest expansion	Percussion note ↓ duller ↑ hyper-resonant	Breath sounds ↑ louder ↓ softer	Added sounds	Vocal resonance
Consolidation		No	Normal or ↓	Normal or ↓	↑ (Bronchial – the best sign)	Coarse crackles +/– rub	↑ Whispering pectoriloquy
Lobar collapse		Yes (towards collapse – the best sign)	↓	↓	↓	No	↓
Pleural effusion		No or away from effusion	↓	↓ (Stony dull – the best sign)	↓	Occasional rub	↓
Pneumothorax		No (without tension) Yes (with tension)	Normal or ↓	↑	↓ (The best sign)	Occasional click	↓

Figure 1.5 Patterns of important focal abnormalities.

SUMMARY BOX – RESPIRATORY SYSTEM EXAMINATION SEQUENCE

- From a distance look for bedside clues, look for cachexia and count the respiratory rate.
- Look at the hands for clubbing, cyanosis or wasting.
- Look at the face for pursed lip breathing or Horner's syndrome.
- Look at the JVP.
- Look at the shape of the chest and chest wall movement and note any use of accessory muscles.
- Feel for tracheal deviation and feel for any lymphadenopathy.
- Assess chest expansion.
- Percuss for areas of dullness (consolidation, collapse, pleural effusion) or hyper-resonance (hyperinflation, pneumothorax).
- Listen to breath sound quality (normal or vesicular) and intensity (reduced in consolidation, collapse, pleural effusion, hyperinflation, pneumothorax).
- Listen for added sounds (crackles, wheeze).
- Listen to vocal resonance (increased in consolidation, decreased in pleural effusion).

Cases

CASE 1.1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Instruction

This 67-year-old woman has been troubled with cough, wheeze and shortness of breath. Please examine her chest and discuss your findings.

Recognition

There may be *tar-stained fingers* (Fig. 1.6), *central cyanosis* (Box 1.3), *pursed lip breathing* and a generally *plethoric* appearance. A *bounding pulse* and *flapping tremor* suggest CO_2 retention.

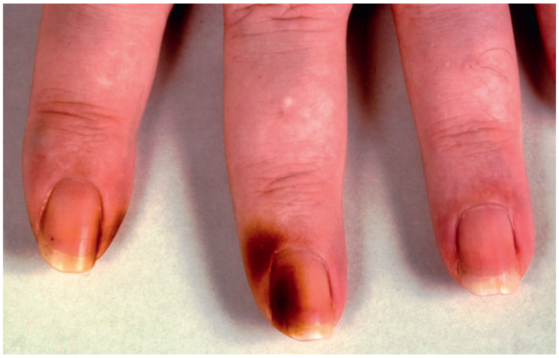


Figure 1.6 Tar staining.

Box 1.3 **Cyanosis**

Cyanosis refers to blue discoloration of skin and mucous membranes and requires a deoxygenated haemoglobin concentration of > 5 g/dl. Thus it does not occur in anaemia. Central cyanosis (blue and warm) is seen at the lips and tongue and occurs in hypoventilation (e.g. chronic obstructive pulmonary disease, neuromuscular disease), V/Q mismatch, impaired gas transfer (e.g. pulmonary oedema) and right-to-left cardiac shunts. Peripheral cyanosis (pink lips, cool peripheries) is the result of local vascular effects and occurs in shock and peripheral vascular disease.

Box 1.4 **Signs of hyperinflation**

- Increased anteroposterior chest diameter ('barrel chest')
- Indrawing of the intercostal muscles and supraclavicular fossae
- Flattening of the subcostal angle
- A shortened cricoid–notch distance (normally greater than three finger-breadths)
- Decreased chest expansion
- Attenuation of heart and liver dullness (with diminished heart sounds)
- Hyperresonance

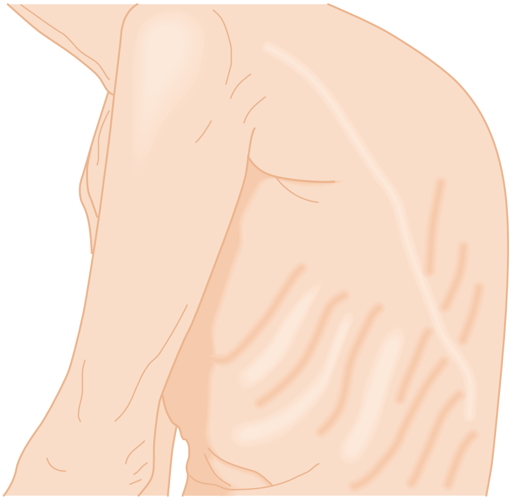


Figure 1.7 'Barrel chest' and intercostal indrawing of chronic obstructive pulmonary disease.

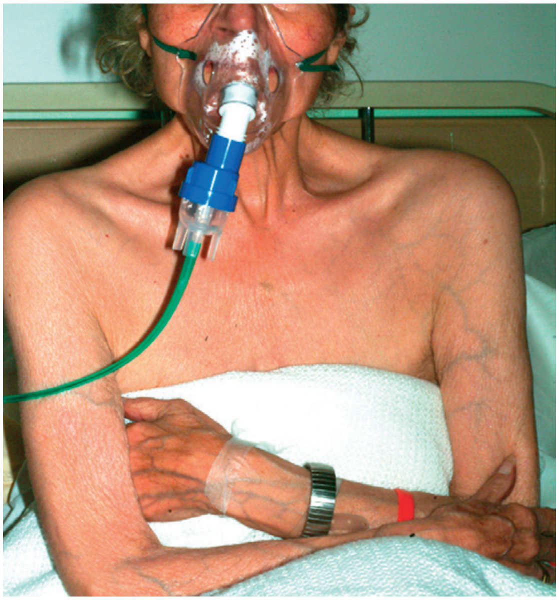


Figure 1.8 Chronic obstructive pulmonary disease cachexia.

Chest

There are signs of *hyperinflation* (Box 1.4, Fig. 1.7), but many patients have a degree of cachexia from chronic disease (Fig. 1.8). There may be an *expiratory wheeze*. Inspiratory crackles suggest superimposed infection.

Interpretation

Confirm the diagnosis

Tell the examiners you would perform spirometry. National Institute for Health and Clinical Excellence (NICE) recommendations for diagnosing chronic obstructive pulmonary disease (COPD) are as follows:

- COPD should be considered in patients aged over 35 years with a risk factor (generally smoking) and exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze (without features of asthma – unproductive cough, nocturnal/diurnal or variable symptoms).
- Post-bronchodilator spirometry should be measured to confirm the diagnosis of COPD.
- Alternative diagnoses or investigations should be considered in older people without typical symptoms of COPD where the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital

capacity (FVC) is < 0.7 or in younger people with symptoms of COPD where the FEV_1/FVC ratio is ≥ 0.7.

What to do next – consider causes

Smoking is by far the commonest cause, confirmed by tar staining; α-antitrypsin deficiency causes lower zone emphysema.

Consider severity / decompensation / complications

Tell the examiners that you would be alert to cor pulmonale (right-sided heart failure due to pulmonary hypertension in chronic lung disease) and CO_2 retention (type 2 respiratory failure). Extrapulmonary complications of COPD are given in Box 1.5, and adversely affect health status, functional capacity and survival.

Consider function

Disability in COPD can be poorly reflected in the FEV_1. A more comprehensive assessment of severity includes the degree of air-flow obstruction and disability, the frequency of exacerbations, and the following known prognostic factors: breathlessness (Medical Research Council dyspnoea scale, Box 1.6), health status, body mass index, cor pulmonale, FEV_1, exercise capacity (for example, 6-minute walking test), transfer factor for carbon monoxide and partial pressure of oxygen in arterial blood.

Box 1.5 **Extrapulmonary complications of chronic obstructive pulmonary disease**

- Skeletal muscle dysfunction due to reduced physical activity, hypoxia, inflammation and smoking (cachexia in advanced disease, but may also be due to malignancy)
- Osteoporosis due to reduced physical activity, inflammation, smoking and corticosteroids
- Cardiovascular disease due to smoking, vascular dysfunction, neurohumeral activation and hyperinflation
- Cognitive dysfunction due to hypoxia, systemic inflammation, smoking and depression

Box 1.6 **Functional scale for breathlessness**

- I only get breathless with strenuous exercise
- I get short of breath when hurrying on the level or walking up a slight hill
- I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
- I stop for breath after walking about 100 yards or after a few minutes on the level
- I am too breathless to leave the house or breathless when dressing or undressing

Discussion

What do you understand by the term chronic obstructive pulmonary disease (COPD)?

COPD is a chronic, progressive disease characterised by signs of air-flow obstruction and obstructive lung disease on spirometry. There is minimal reversibility with bronchodilators. The terms chronic bronchitis and emphysema are sometimes used synonymously. Over 3 million people in the UK are estimated to have COPD, the majority still undiagnosed.

Chronic bronchitis

This is defined clinically (UK Medical Research Council) as chronic, productive cough for at least 3 months of two consecutive years in the absence of other diseases causing sputum production. Mucus hypersecretion results from gland hypertrophy and increased goblet cell numbers. Large airways (bronchitis) and small airways (bronchiolitis) are affected in continuum.

Emphysema

This is defined pathologically as permanent enlargement of airways distal to the terminal bronchiole. There is destruction of their walls without obvious fibrosis. It may be predominantly centriacinar (destruction of alveoli at the centre of the acini, especially associated with smoking and affecting upper lobes), panacinar, paraseptal or localised around scars. Bullae are large emphysematous spaces > 1 cm in diameter.

Development of pulmonary hypertension

Chronic bronchitis and emphysema overlap and pulmonary vasculature changes – intimal and medial thickening, smooth muscle proliferation and inflammatory cell infiltration – with hypoxaemia and vasoconstriction lead to pulmonary vascular remodelling and ultimately sustained pulmonary hypertension.

What is the pathogenesis of COPD?

This is related to the inflammatory response to environmental triggers, an imbalance between proteinases and antiproteinases and an imbalance between oxidants and antioxidants.

What is one smoking pack year?

One pack year is equivalent to smoking 20 cigarettes a day for 1 year.

List some causes of COPD other than smoking

- α_1-antitrypsin deficiency
- Environmental (short-term exposure to high-level particulate air pollution correlates with exacerbations)

- Occupational, e.g. coal workers, cadmium workers
- Genetic polymorphisms (probably determine susceptibility to environmental causes)

What is α_1-antitrypsin deficiency?

α_1-antitrypsin is a protease inhibitor (Pi) enzyme, synthesised in the liver during the acute-phase response, which inhibits neutrophil elastase. Low levels of the enzyme, determined by various genotypes (PiZZ the most severe with enzyme levels < 10% of those with normal M alleles), fail to protect the lung from proteolytic attack, resulting in destruction of alveolar walls, particularly in times of infection when vigorous elasteolytic activity is unopposed. This ultimately results in basal, panlobular emphysema, accelerated in smokers, and cirrhosis. Patients typically present in the fourth or fifth decades.

How may the diagnosis of COPD be confirmed?

A post-bronchodilator $FEV_1 < 80\%$ of the predicted value with a ratio of $FEV_1 : FVC < 70\%$ that is not fully reversible is consistent with COPD.

List some other tests that you might consider in assessing a patient with COPD

- Full blood picture (polycythaemia)
- Arterial blood gases (ABGs)
- Chest X-ray (hyperinflation, bullae, prominent pulmonary vessels)
- Electrocardiogram (p pulmonale, right axis deviation, right bundle branch block)

How might you grade COPD severity?

The Global Initiative for Chronic Obstructive Lung Disease classification and NICE staging based on FEV_1 (Table 1.2) align with international guidelines and are prognostically informative.

What management options are there in stable COPD?

Specialist referral

This may be appropriate at all stages of the disease. Indications include diagnostic uncertainty, rapidly changing disease (both on spirometry and in symptoms) and onset of complications such as cor pulmonale.

Smoking cessation

All patients should be encouraged to stop smoking. Unless contraindicated, nicotine replacement therapy (varenicline or bupropion) should be offered, together with a support programme.

Inhaled therapy

A NICE clinical algorithm provides an evidence-based rationale for the sequencing of inhaled drugs used singly and in combination according to persistence of symptoms, exacerbations, and severity of air-flow obstruction (Fig. 1.9) and clarifies options for escalating inhaled treatment according to whether FEV_1 is above or below 50%.

Oral therapies

Maintenance oral corticosteroid therapy in COPD is not normally recommended. Theophylline may be offered only after trials of short- and long-acting bronchodilators or to people who cannot use inhaled therapy. It can be used in combination with β_2-agonists and muscarinic antagonists. Dose reduction is needed with macrolide or fluroquinolone antibiotics. Mucolytic therapy may be used for chronic productive cough if symptoms improve, but not routinely to prevent exacerbations.

Table 1.2 The Global Initiative for Chronic Obstructive Lung Disease and National Institute for Health and Clinical Excellence classification of chronic obstructive pulmonary disease (COPD) (when the post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) is < 0.7)

Stage	At risk	I	II	III	IV
		Mild*	Moderate	Severe	Very severe**
FEV_1 (% of predicted)	Normal spirometry (FEV_1 / FVC > 0.7)	≥ 80	50–79	30–49	< 30
Characteristics	Chronic symptoms + risk factors	With or without symptoms	With or without symptoms	With or without symptoms	Chronic respiratory failure or right-sided heart failure (cor pulmonale)
Stepwise treatments	Avoidance of risk factors Influenza vaccination	Add inhaled short-acting bronchodilator when needed	Add inhaled regular bronchodilator(s) Rehabilitation	Add inhaled regular glucocorticoid if repeated exacerbations	Add LTOT if chronic respiratory failure Consider surgical treatments

LTOT, long-term oxygen therapy. *Symptoms should be present to diagnose COPD in people with mild air-flow obstruction. **Or when $FEV_1 < 50\%$ is accompanied by respiratory failure.

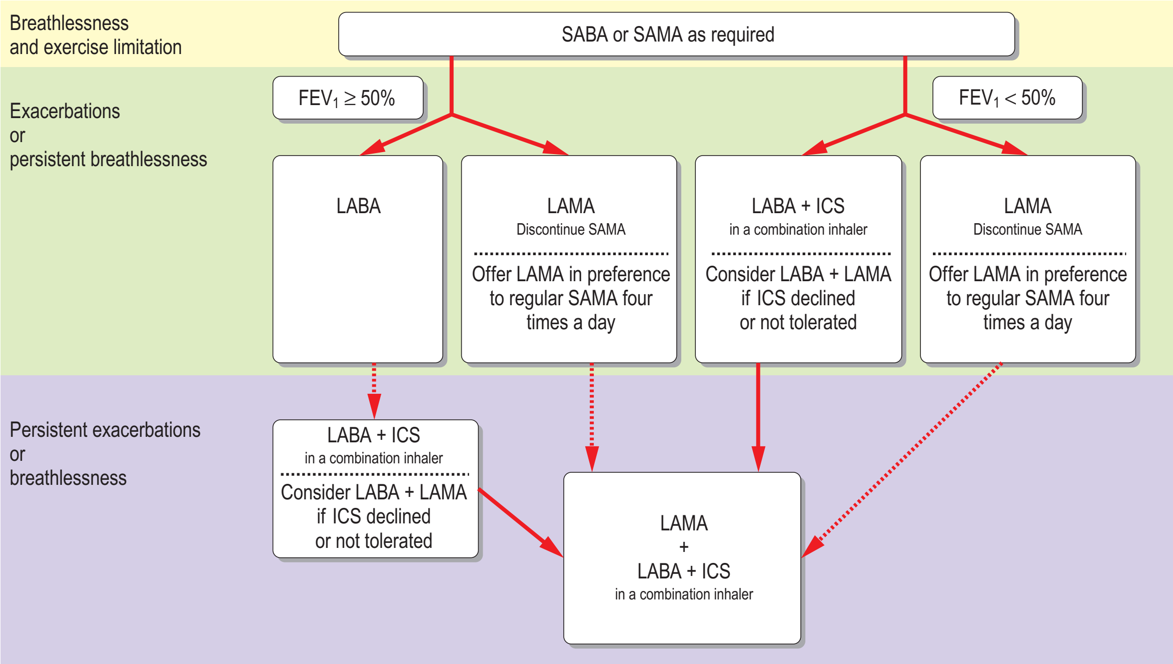

Breathlessness and exercise limitation
SABA or SAMA as required
Exacerbations or persistent breathlessness
FEV$_1$ ≥ 50%
FEV$_1$ < 50%
LABA
LAMA
Discontinue SAMA
Offer LAMA in preference to regular SAMA four times a day
LABA + ICS
in a combination inhaler
Consider LABA + LAMA if ICS declined or not tolerated
LAMA
Discontinue SAMA
Offer LAMA in preference to regular SAMA four times a day
Persistent exacerbations or breathlessness
LABA + ICS
in a combination inhaler
Consider LABA + LAMA if ICS declined or not tolerated
LAMA + LABA + ICS
in a combination inhaler

Figure 1.9 Inhaled therapy in chronic obstructive pulmonary disease. Inhaled corticosteroid (ICS) is recommended only in a combination inhaler. The evidence for a long-acting beta agonist (LABA) plus ICS over LABA is strong in severe or very severe air-flow obstruction (forced expiratory volume in 1 second (FEV$_1$) < 50%) but weaker with mild or moderate air-flow obstruction (FEV$_1$ ≥ 50) with recommendation for LABA + ICS treatment only if symptoms persist with LABA alone. Limited evidence for adding LABA plus ICS in those still symptomatic despite LAMA led to a recommendation for triple therapy only in this situation. Adding LAMA to LABA plus ICS (triple therapy) to people who remain breathless or have exacerbations despite taking LABA plus ICS irrespective of FEV$_1$, is based on stronger evidence. LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; SAMA; short-acting muscarinic antagonist. *(From NICE 2010 Chronic Obstructive Pulmonary Disease (partial update), replacing NICE clinical guideline 12, with permission.)*

Pulmonary rehabilitation

This should be offered to all patients who consider themselves functionally disabled by COPD, including following admission for an acute exacerbation, but is not suitable for patients who are unable to walk, have unstable angina, or had a recent myocardial infarction.

Vaccination

Annual influenza vaccination and 5- to 10-year pneumococcal vaccination are important.

How can treatment response be assessed in stable COPD?

There is often minimal improvement in spirometry. Short-term changes in FEV$_1$ in response to bronchodilators or steroids are poor predictors of symptomatic benefit in moderate to severe COPD. Symptomatic improvement is more useful, e.g. reduced breathlessness, increased exercise capacity and improved sleep.

Is there a role for surgery in COPD?

Lung volume reduction surgery may increase exercise capacity by reducing dynamic hyperinflation, improving diaphragmatic function and improving elastic recoil and may be useful for large bullae, especially upper lobe disease. Surgery is contraindicated with FEV$_1$ < 20% or if emphysema is homogeneous.

What are the indications for long-term oxygen therapy (LTOT), ambulatory oxygen therapy and short-burst oxygen therapy?

COPD

LTOT is indicated for managing respiratory failure in stable COPD and is one of few interventions shown to improve survival in COPD. Oxygen is administered via nasal cannulae at 2–4 l/min via a concentrator for at least 15 hours a day, aiming for $paO_2 > 8$ kPa. Patients must not smoke! Eligibility criteria are shown in Box 1.7.

Those on ambulatory oxygen may be classified into those with low activity who are usually immobile and require the same flow rate as their LTOT and those who are active who desaturate on exercise, some of whom are on LTOT. Short-burst oxygen therapy for breathless patients is not evidence based.

Box 1.7 **Indications for long-term oxygen therapy**

- $p_aO_2 < 7.3$ kPa (55 mmHg) on air
- p_aO_2 7.3–8.0 kPa (55–60 mmHg) if there is pulmonary hypertension or nocturnal hypoxaemia
- $FEV_1 < 1.5$ litres

Arterial blood gases should be measured when clinically stable and on two occasions at least 3 weeks apart (PO_2 should rise with treatment above 8 kPa without unacceptable hypercapnia).

Other conditions

Conditions other than COPD considered suitable for LTOT and ambulatory oxygen therapy include severe chronic asthma, interstitial lung disease (ILD), cystic fibrosis (CF) and pulmonary vascular disease. Conditions suitable for LTOT but not ambulatory oxygen therapy include bronchiectasis, pulmonary malignancy and heart failure. Conditions of hypoventilation are better managed with non-invasive ventilation.

How do acute exacerbations of COPD arise?

Most exacerbations are triggered by tracheobronchial infection with viruses (rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, influenza) or bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Pseudomonas aeruginosa, Chlamydia pneumoniae*). Some pollutants are triggers. Triggers activate transcription factor NF-KB in airway epithelial cells and macrophages. These cells release inflammatory cytokines both within the airway and systemically including the neutrophil chemoattractant interleukin (IL)-8 (CXCL-8), and tumour necrosis factor-α and interleukin-6 (IL-6), which amplify inflammation. C-reactive protein (CRP) rises are often sensitive markers of COPD exacerbations.

How does an acute exacerbation of COPD (AECOPD) lead to type 2 respiratory failure?

Alveolar ventilation (i.e. the volume of useful air exchanged) refers to minute ventilation (the total volume of air moving in and out of the lungs per minute, given by tidal volume × respiratory rate) minus the dead space (the proportion of minute ventilation trapped in the lungs). Dead space is increased in COPD because of expiratory air-flow obstruction that is only partially compensated for by increased expiratory time, leading to hyperinflation. This ultimately leads to decreased muscle function, flattening of the diaphragm from its optimum dome shape and failure of the intercostal muscles to exert adequate upward pull. This leads to intrinsic positive end expiratory pressure (PEEP); normally, resting pressure is atmospheric but in COPD it is always greater, causing positive airway pressure, a situation demanding extra work to get air into the lungs. Tidal volume ultimately decreases and the respiratory rate must increase to compensate, creating a vicious cycle because an increased respiratory rate exacerbates gas trapping with worsening type 2 respiratory failure.

How would you manage acute respiratory failure in COPD?

Controlled oxygen therapy and supportive ventilation (non-invasive ventilation or invasive mechanical ventilation) aim to prevent tissue hypoxia and control acidosis and hypercapnia while medical therapy maximises lung function and reverses any precipitating cause. Antibiotics have a role in acute exacerbations of COPD but not stable COPD, as do nebulisers.

Intravenous aminophylline fell from favour following a Cochrane review demonstrating its failure to increase FEV_1 or shorten hospital admission, while at the same time increasing adverse effects. Oral prednisolone 30 mg is generally given for 7–14 days and then stopped. Assessment for LTOT should occur 6 weeks after an exacerbation.

The best marker of severity is pH; it reflects acute deterioration in alveolar hypoventilation (acute rise in p_aCO_2) compared with the chronic stable state. A pH of < 7.26 is associated with 30% mortality.

Increases in p_aCO_2 are associated with significant mortality but the absolute p_aCO_2 and p_aO_2 are less significant than pH; for example, a p_aCO_2 of 8.5 kPa associated with a bicarbonate of 35 mmol/l and a normal pH might merely reflect chronic respiratory acidosis with metabolic compensation whereas a p_aCO_2 of 9 kPa with a normal bicarbonate and low pH more likely reflects acute decompensation.

Some typical ABG results are shown in Table 1.3.

Oxygen therapy

Oxygen delivery vital for organ function relies upon adequate total blood oxygen content, adequate haemoglobin to carry it, and cardiac output. Because of the steep slope of the oxyhaemoglobin dissociation curve at tissues, falls in oxygen delivery are offset by increased oxygen extraction. Normal p_aO_2 is 10–13kPa and oxygen delivery cannot be significantly enhanced by increasing p_aO_2 above 16 kPa where haemoglobin is fully saturated. Maximising oxygen saturation not only fails to optimise tissue oxygenation but also may cause adverse physiological effects. The best example of this is in AECOPD in which p_aO_2 above 10 kPa is associated with respiratory acidosis and CO_2 narcosis and worse outcomes; the mechanisms are likely decreased hypoxic drive, absorption atelectasis, the Haldane effect (decreased CO_2 buffering by oxyhaemoglobin) and, probably the greatest contributor, release of hypoxic pulmonary vasoconstriction promoting worsening ventilation–perfusion mismatch – usually alveolar hypoxia due to poor ventilation causes vasoconstriction and so deoxygenated pulmonary artery blood is diverted from diseased lung but with hyperoxia these alveoli are re-oxygenated and re-perfused but remain poorly ventilated and cannot clear CO_2. In relatively healthy lungs, regional hypoventilation may be compensated for by overall increased ventilation, but this is not possible in

Table 1.3 Typical arterial blood gas (ABG) results and action needed

	Normal	Unwell (non-respiratory illness)	Stable COPD	Acutely unwell COPD	Acutely unwell COPD
p_aO_2 (kPa)	10–13	9	8	8	6
p_aCO_2 (kPa)	5	6	8	8	9.5
pH	7.4	7.2	7.4	7.3	7.25
HCO_3	26	24	34	24	18
Action needed	None	Treat underlying cause	None if patient well	Consider non-invasive ventilation (NIV)	Consider NIV or ITU / invasive ventilation

COPD. Other adverse effects of hyperoxia include coronary vasoconstriction and neuronal injury (especially damaging in stroke).

Guidelines for oxygen therapy in acute situations recommend high-concentration oxygen when monitoring is unavailable (pre-hospital) and in critical illness, but oxygen only to maintain normal oxygen saturations in most monitored situations. This means:

- In those at risk of hypercapnic respiratory failure, starting with a 24% or 28% Venturi mask and aiming for oxygen saturation 88–92%
- In those not at risk of hypercapnic respiratory failure with saturations ≥ 85% starting with nasal cannulae (2–6 l/min) or face mask (5–10 l/min) and aiming for oxygen saturation 94–98%
- In those not at risk of hypercapnic respiratory failure with saturations < 85% using a reservoir or bag–valve mask.

Non-invasive positive pressure ventilation (NIV)

NIV in COPD is outlined in Box 1.8.

Can NIV be used in other conditions?

- In AECOPD the evidence is robust. NIV improves pH, pCO_2 and respiratory rate in the first hour, reduces treatment failure, reduces intubation, reduces complications (likely to be a consequence of avoiding intubation, which increases infection), reduces mortality (likely to be a consequence of reduced complications) and reduces length of stay. In the subsequent 12 months, however, 80% of patients are re-admitted, 63% have a life-threatening episode and 50% die.
- In acute pulmonary oedema (APO), NIV as continuous positive airway pressure (CPAP) promotes earlier improvement of dyspnoea and metabolic abnormalities but does not improve survival; it should be considered as adjunctive therapy in those with respiratory distress or not responding to pharmacological measures.
- In acute hypoxaemic respiratory failure (AHRF) evidence is controversial.
- In immunocompromised patients NIV may be used in human immunodeficiency virus-related pneumocystic pneumonia with renal failure, haematological malignancy, solid tumours and organ transplantation, with evidence of benefit.
- In asthma NIV may be used by those with considerable NIV expertise, but only where there is a very low threshold for intubation in the event of deterioration.
- In patients 'not for ICU or for DNAR', factors favouring a survival advantage include COPD, APO, a strong cough and alertness, whilst pneumonia, cancer and other diagnoses fare less favourably.
- NIV is sometimes used when weaning from mechanical ventilation, in extubation failure, in postoperative respiratory failure, in acute exacerbations of restrictive lung disease in CF and in trauma.

Which factors are associated with a favourable outcome from NIV?

Factors associated with successful NIV include moderate pCO_2 (6–13 kPa), moderate acidaemia (pH > 7.3), a good level of consciousness, younger age, an acute physiology and chronic health evaluation (APACHE) score < 20, and tolerance. The best predictor of a good outcome is physiological improvement in pH, pCO_2 and respiratory rate after 1 or 2 hours.

Factors associated with NIV failure include the opposites of these, multi-organ failure, pneumonia, acute respiratory distress syndrome (ARDS), and poor nutritional status.

What is cor pulmonale?

This is ventricular enlargement and failure occurring secondary to lung/chest wall/pulmonary circulatory disease. Central to cor pulmonale development is pulmonary hypertension. The 5-year mortality in patients with COPD who develop peripheral oedema is 70–100%.

Box 1.8 **Non-invasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD)**

NIV is indicated for acute exacerbations of COPD with respiratory failure, and also other conditions including chest wall disease and obesity hypoventilation syndrome.

Patient selection

NIV should be considered in an acute exacerbation of COPD where respiratory acidosis ($pH < 7.35$, $pCO_2 > 6$ kPa) persists despite immediate maximum standard medical treatment (nebulised salbutamol 2.5–5 mg and ipratropium 500 μg, prednisolone 30 mg, antibiotics if appropriate) on controlled oxygen for no more than 1 hour. Acidosis is the key determinant of NIV. Based on pre-morbid state, severity, reversibility, the presence of relative contra-indications and patient wishes where possible, patients should be stratified into:

1. Requiring immediate intubation and ventilation and intensive care
2. Suitable for NIV and for escalation to 1
3. Suitable for NIV but not suitable for 1
4. Not suitable for NIV but suitable for full active medical management
5. Palliative care agreed as most appropriate.

Absolute contraindications to NIV include fixed upper airway obstruction, facial trauma or burns, and vomiting. Most other contraindications such as secretions, impaired consciousness, pneumothorax and haemodynamic instability are relative.

Early studies demonstrated that in sicker patients with $pH < 7.25$ NIV was not a substitute for intubation, ventilation and intensive care because mortality was around 30%; however, the greater usage and experience with NIV has lowered this threshold to < 7.25 in the eyes of many experts. Of course, not all NIV environments, expertise, and equipment are the same.

How NIV works

NIV is delivered via a tightly fitting face-mask with humidifier and a bi-level positive airway pressure (BIPAP) box with or without oxygen. NIV overcomes auto-positive end-expiratory pressure (auto-PEEP) and reduces inspiratory effort. It is patient triggered. The patient initiates a breath and the box kicks in to raise inspiratory positive airway pressure (IPAP) to a set reading. The patient learns to 'relax' into what at first may be an uncomfortable apparatus. Expiratory positive airway pressure (EPAP) = PEEP and IPAP can be balanced with a small amount of PEEP. Oxygen can be entrained to maintain saturations between 85% and 92%. BIPAP is different to continuous positive airway pressure (CPAP), which delivers 5–10 cmH_2O throughout the breathing cycle. IPAP, by providing positive airway pressure, assists ventilation, while EPAP recruits underventilated lung and improves the ventilation–perfusion ratio as well as reducing rebreathed air by eliminating exhaled air via the expiratory port.

Set-up

Patients should be capable of protecting their airway and cooperative, sitting or semi-recumbent. The following are recommended:

- A full-face mask for the first 24 hours followed by a switch to a nasal mask if preferred by the patient
- Initial IPAP of 10 cmH_2O and EPAP of 4–5 cmH_2O, tolerated by most patients
- IPAP increased by 2–5 cm increments at a rate of 5 cmH_2O every 10 minutes with a target of 20 cmH_2O or until therapeutic response; EPAP generally unaltered as higher pressures are rarely tolerated
- Oxygen when needed entrained into the circuit and flow adjusted to achieve target saturation, usually 88–92%
- Bronchodilators preferably administered off NIV.

Monitoring and escalation

- Baseline arterial blood gas (ABG) analysis, respiratory rate and heart rate
- Continuous pulse oximetry
- Repeated ABGs at 1 hour and 1 hour after every subsequent change in settings
- Frequent clinical monitoring of acutely ill patients – respiratory rate, heart rate, conscious level, chest wall movement, ventilator synchrony, accessory muscle use – every 15 minutes in the first hour, every 30 minutes in the 1–4-hour period and hourly in the 4–12-hour period

As a very general rule, $pH < 7.3$ should provoke an adjustment in NIV settings and consideration of intensive care if the patient is suitable (a decision for intensive care involvement should usually be within the first few hours), pH 7.30–7.35 suggests continuing NIV (80% chance of improvement) and $pH > 7.35$ suggests improvement and provokes consideration of stopping NIV.

Duration

Patients who benefit from NIV in the first 4 hours should receive it for as long as possible (minimum of 6 hours) in the first 24 hours.

Weaning

Weaning should be in daytime hours, and the following is recommended: NIV for 16 hours on day 2; NIV for 12 hours on day 3 including 6–8 hours overnight; NIV discontinued on day 4.

CASE 1.2 CONSOLIDATION

Instruction

This patient is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There may be *tachypnoea*. There may be *reduced expansion on the affected side* but the *trachea is central*. There is *dullness* to percussion over one or more lobes (Fig. 1.10). There are *bronchial breath sounds* (+/− *coarse crackles*) and *vocal resonance is increased* over the affected lobe(s). There may be *whispering pectoriloquy* and a *pleural friction rub*.

Interpretation

Confirm the diagnosis

The main differential diagnoses are pleural effusion and collapse:

- A pleural effusion produces stony dullness on percussion, reduced breath sounds and reduced vocal resonance.
- Collapse may cause the trachea to deviate towards the affected side.

What to do next – consider causes

The commonest cause is pneumonia (breathlessness, pyrexia, purulent sputum). Lung cancer with distal infection should always be considered (clubbing, cachexia).

Consider severity / decompensation / complications

Tell the examiners you would determine the CURB score (Case 1.4).

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

What is whispering pectoriloquy?

Whispered sounds are heard clearly on auscultation, confirming consolidation because a whispered voice is clearly audible through solid lung, just as vocal resonance is increased in consolidation.

CASE 1.3 DULLNESS AT THE LUNG BASE

Instruction

This patient is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There may be *tachypnoea*. There may be *reduced expansion on the affected side* but the *trachea is central*. There is *dullness* to percussion at the lung base (Fig. 1.11).

Interpretation

Confirm the diagnosis

The main differential diagnoses are pleural effusion, consolidation and collapse:

- A pleural effusion produces stony dullness on percussion, reduced breath sounds and reduced vocal resonance.
- Consolidation produces dullness to percussion, bronchial breath sounds, increased vocal resonance and whispering pectoriloquy.
- Collapse may cause the trachea to deviate towards the affected side.

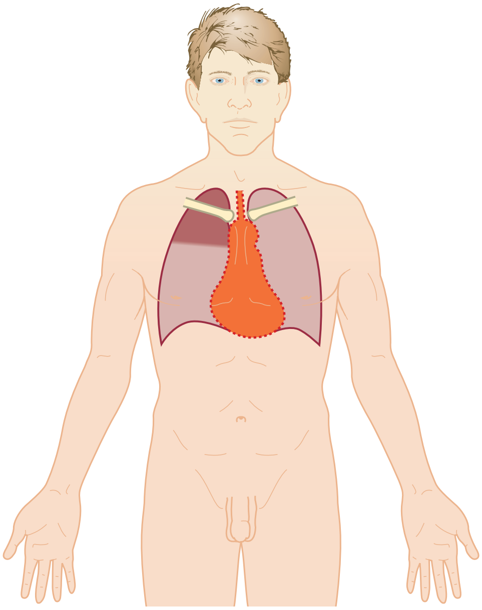


Figure 1.10 Consolidation.

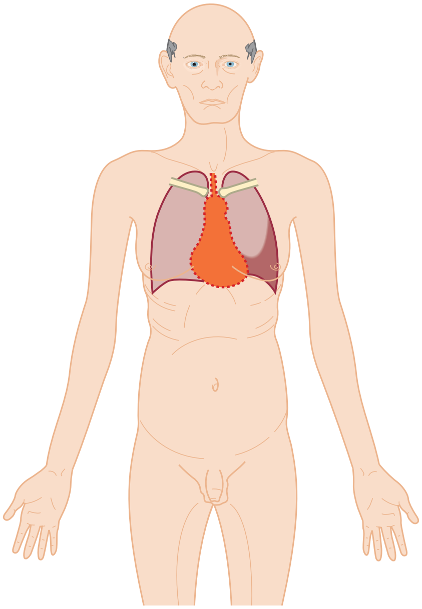


Figure 1.11 Dullness at the lung base.

What to do next – consider causes

Unilateral pleural effusions are often exudates (parapneumonic, lung cancer); if a pleural effusion seems likely, tell the examiners you would aspirate it (after chest X-ray) to differentiate causes. Tell the examiners that common causes of consolidation or collapse are pneumonia and lung cancer.

Consider severity / decompensation / complications

If consolidation seems likely, tell the examiners you would consider pneumonia and determine the CURB score (Case 1.4) but also wish to exclude malignancy.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

List some causes of dullness at the lung base

- Pleural effusion
- Consolidation
- Collapse
- Raised hemidiaphragm, e.g. hepatomegaly, phrenic nerve palsy
- Pleural thickening

CASE 1.4 PNEUMONIA

Instruction

This patient is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There may be *tachypnoea*. There may be *reduced expansion on the affected side* but the *trachea is central*. There is *dullness* to percussion over one or more lobes (Fig. 1.12). There are *bronchial breath sounds* (+/− *coarse crackles*) and *vocal resonance is increased* over the affected lobe(s). There may be *whispering pectoriloquy* and a *pleural friction rub*.

Interpretation

Confirm the diagnosis

Pyrexia and rigors may or may not be present.

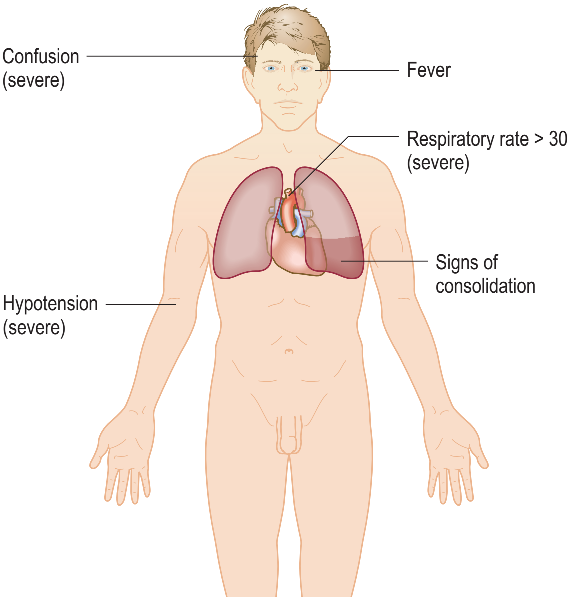


Figure 1.12 Pneumonia.

Box 1.9 CURB-65 score

- Confusion (abbreviated mental test score ≤ 8/10)
- Urea > 7 mmol/l
- Respiratory rate ≥ 30/minute
- Blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg)
- 65 – age > 65 years

What to do next – consider causes

Streptococcus pneumoniae is the commonest pathogen in community-acquired pneumonia (CAP), even in patients with chronic obstructive pulmonary disease (COPD), followed by *Haemophilus influenzae* in older people. Other pathogens include ‘atypical organisms’ (especially in younger people), *Staphylococcus aureus*, *Moxarella catarrhalis* and influenza viruses A and B (especially in older people), Gram-negative bacteria and anaerobic bacteria (aspiration). Organisms are not isolated in up to half of cases. Streptococcal pneumonia is more common in winter. It is characterised by its abrupt onset and often causes high fever and rigors. Lobar consolidation is typical. Herpetic cold sores are common. Vaccination is recommended for high-risk patients.

Consider severity / decompensation / complications

Tell the examiners you would determine the CURB score. The CURB-65 score stratifies patients into different prognostic groups suitable for different management pathways (Box 1.9, Table 1.4). Other signs of serious infection associated with a poor prognosis that do not enter the CURB score include albumin < 30 g/l, white cell count < 4 or > 20 × 10^9/l, severe hypoxia and multilobar

Table 1.4 CURB-65 score prognosis and management

CURB-65 score	Mortality (%)	Management
0 or 1	1.5	Home treatment likely
2	9.2	Short admission likely
≥ 3	22	Hospital management for severe pneumonia ITU possible if CURB-65 score ≥ 3

Box 1.10 **Possible complications of pneumonia**

- Respiratory failure
- Pleural effusion (common)
- Empyema (less common) associated with treatment failure, persistent fevers, malaise and weight loss
- Lung abscesses (rare)
- Cavitation
- Fibrosis

or bilateral disease. The CURB score is a guide, and a low CURB score can sometimes be falsely reassuring.

Possible complications are listed in Box 1.10.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

What types of lower respiratory tract infection (LRTI) are there?

These include cough with sputum (acute bronchitis), acute exacerbations of COPD, CAP and atypical pneumonia.

When might you treat acute bronchitis with antimicrobial therapy?

Acute bronchitis is common after upper respiratory tract infection and is usually self-limiting. Pathogens are similar to those in CAP. Antimicrobials are indicated if there is clinical deterioration or if focal chest signs develop.

When might you treat an acute exacerbation of COPD with antimicrobial therapy?

An acute exacerbation of COPD may be defined as increased cough, sputum and dyspnoea without focal signs. The pathogen is usually viral. The British Thoracic Society recommends antimicrobials if two or more of worsening dyspnoea, increased sputum purulence or increased sputum volume are present.

What is pneumonia?

Pneumonia is an inflammatory, usually infectious, disease of lung parenchyma. Most is managed in primary care. The most common symptoms are cough, sputum, dyspnoea and pleuritic pain. The most common signs are fever, tachypnoea, tachycardia and signs of consolidation. The presentation may be different in the elderly, such as confusion.

How common is community-acquired pneumonia (CAP)?

The annual incidence is six per 1000 population in the 16–59-year age group rising to 34 per 1000 population in those aged 75 and over. Hospital admission is required in 20–40% of cases and of those 5–10% need admission to ITU.

What investigations would you consider in pneumonia?

Initial tests are routine haematobiochemistry and chest X-ray. In severe CAP blood cultures are important, and urine rapid testing for pneumococcal and *Legionella* antigens may be useful. Polymerase chain reaction (PCR) testing of sputum and serology may be performed for other suspected organisms.

What would be your empirical first-line antibiotic for CAP?

Local guidelines vary and evolve quickly. Generally, amoxicillin remains the preferred choice for patients without severe pneumonia and without penicillin hypersensitivity. Hospitalised patients may receive 7 days of oral amoxicillin together with a macrolide, doxycycline or a fluoroquinolone (enhanced pneumococcal activity may be provided by levofloxacin or moxifloxacin). A β-lactam antibiotic or non-first-generation cephalosporin, with a macrolide, is indicated in severe pneumonia, when therapy should be intravenous initially and for at least 10 days. Rifampicin may be added in *Legionella* infection. The 'Gram-positive' fluoroquinolones (levofloxacin, moxifloxacin) should not be used as first-line therapy but may be useful in penicillin allergy or if there is local concern regarding *Clostridium difficile* diarrhoea with β-lactam use.

When should a patient be discharged from hospital following pneumonia?

When clinically stable, and without signs of clinical instability (Box 1.11); radiographic resolution occurs in 50% at 2 weeks and 70% at 6 weeks and is slower in older people. All patients should be reviewed 6 weeks after discharge. Smokers, those over 50 or those with persistent symptoms should have a follow-up chest X-ray, and persisting changes investigated.

These features are all associated with a high re-admission rate and mortality.

Which individuals should have the pneumococcal vaccine?

Department of Health recommendations include those aged over 65 years, asplenic patients or those with splenic dysfunction (e.g. coeliac disease), patients with chronic respiratory, heart, renal or liver conditions, immunosuppressed patients, those with cochlear implants and those with cerebrospinal fluid leaks.

Which individuals should receive the influenza vaccine?

Target groups based on increased susceptibility include those in institutional care, those with chronic disease (e.g. heart disease, lung disease, cancer, immune deficiency, renal disease, diabetes, liver disease) and those aged over 65 years. Vaccination of health-care workers and those caring for the elderly is recommended.

Box 1.11 **Signs of clinical instability in pneumonia**

- Temperature > 37.8°C
- Heart rate > 100
- Respiratory rate > 24
- Systolic blood pressure < 90 mmHg
- Oxygen saturation < 90%
- Abnormal mental state
- Inability to take oral medication

These features are all associated with a high re-admission rate and mortality.

How does atypical pneumonia present?

The spectrum of disease ranges from asymptomatic infection to severe hypoxic respiratory failure requiring ventilatory support. Atypical pneumonia often affects young adults and there may be a travel history. It tends to produce insidious constitutional symptoms and a paucity of respiratory symptoms after a 10–20-day incubation period. Despite this, chest signs may be present and chest radiography may be impressive, often with bilateral infiltrates. Extrapulmonary features are common (Table 1.5).

List some differential diagnoses of unresolving pneumonia

- Bronchial carcinoma
- Empyema
- Lung abscess
- Pulmonary oedema
- Fibrotic lung disease
- Pulmonary emboli

What is a parapneumonic effusion and how does it differ from empyema?

These are discussed in Case 1.21.

What cavitating lung conditions do you know?

A lung abscess causes cavitation with an air–fluid level. Common cavitating organisms include *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Mycobacterium*

Table 1.5 Features of atypical pneumonias

Extrapulmonary features shared by atypical pneumonias	Specific organism	Epidemiology	Clinical features
Arthralgias and myalgias Autoimmune haemolytic anaemia (usually mild) due to cold agglutinins, common in *Mycoplasma* Maculopapular rash, erythema multiforme, Stevens–Johnson syndrome, erythema nodosum Bullous myringitis (*Mycoplasma*) Sterile meningitis, meningoencephalitis, transverse myelitis, cranial neuropathies, peripheral mononeuropathies, Guillain–Barré syndrome Myocarditis / pericarditis Hepatitis	*Mycoplasma pneumoniae*	Younger adults Epidemics every few years	Non-productive cough (paroxysms common) invariably Paucity of signs compared with symptoms and chest X-ray appearances
	Legionella pneumophila	Gram-negative bacillus preferring stagnant water Legionnaire's disease more common with pre-existing lung disease	Pontiac fever – acute self-limiting febrile illness Legionnaire's disease – diarrhoea, abdominal pain, abnormal liver function and headaches before respiratory symptoms Peripheral cytopenias Renal failure
	Chlamydia pneumoniae	Older adults	Extrapulmonary features less common
	Chlamydia psittaci	Classically transmitted from birds Human-to-human transmission possible	Often presents with severe headache
	Coxiella burnettii	Usually transmitted from farm animals (lambs and calves in spring)	Rare Q fever, ranging from asymptomatic infection to severe pneumonia

tuberculosis. Other causes of cavitation include carcinoma, vasculitis and pulmonary infarction.

What is the differential diagnosis of a possible lung abscess on chest X-ray?

- Emphysema with consolidation ('tatty lungs')
- Bronchiectasis with air–fluid levels ('cystic bronchiectasis')
- Empyema
- Pulmonary infarction with secondary cavitation
- Vasculitis
- Hiatus hernia
- Carcinoma
- An old tuberculosis (TB) cavity with an aspergilloma

How might a lung abscess be differentiated from carcinoma?

An abscess is thin-walled, with a marked fluid level, and is often central. A carcinoma is thick walled, with an eccentric cavity.

Which organisms can cause a lung abscess?

These include *Staphylococcus*, *Streptococcus*, *Mycobacterium*, *Legionella*, Gram-negative bacteria (especially post-aspiration) and anaerobes (especially post-aspiration). 'Compost', with multiple types of bacteria, is common.

List some factors associated with the development of a lung abscess

- Increasing age
- Long duration of symptoms
- Influenza A epidemic (staphylococcal pneumonia)
- Source of metastatic infection (shunts, intravenous drug use)
- Aspiration (right lower lobe – always think aspiration in older people or inhaled foreign body in children owing to the more vertical orientation of the right main bronchus)
- Immune compromise
- Underlying lung disease

How is a lung abscess treated?

Drainage, aided by posture and physiotherapy, is important, but specialist care is needed because patients might have to lie in one position for hours and there is a danger of pus draining elsewhere. Antibiotics may include amoxicillin and flucloxacillin in an influenza epidemic, and metronidazole in patients with halitosis.

What do you know about influenza-related pneumonia?

Influenza viruses are members of the Orthomyxoviridae family and subclassified into influenza A, B and C, of which only C has pandemic potential, as demonstrated by the 1918 H1N1 pandemic in which 20–50 million people died worldwide, H1N1 also causing a pandemic in 2009.

Primary influenza pneumonia and post-influenza secondary bacterial pneumonia are separate entities but can be difficult to distinguish clinically. Influenza may also cause superinfection with atypical pathogens, and cardiac (myocarditis, pericarditis), muscular (myositis, rhabdomyolysis) and neurological (encephalopathy, encephalomyelitis, transverse myelitis, aseptic meningitis, Guillain–Barré syndrome) complications.

Primary influenza causes fever and other symptoms including cough, sore throat, rhinorrhoea, joint pains, headache, vomiting or diarrhoea, and may cause life-threatening illness suggestive of an infective process. Diagnosis is by PCR of nasopharyngeal or throat swabs.

Some features favouring secondary bacterial pneumonia over primary influenza pneumonia include latency before respiratory compromise of a few days or secondary fever after a period of defervescence, raised white cell count or inflammatory markers, lobar infiltrates on the chest X-ray rather than bilateral interstitial infiltrates of influenza, and antibiotic responsiveness.

Antiviral drugs are best delivered early for primary influenza, but may be effective up to 7 days after onset.

What new viral lung infections are causing concern?

Viral lung infections with potential to cause large outbreaks of severe respiratory disease include influenza A (H5N1), severe acute respiratory syndrome (SARS) and hantavirus. The H5N1 subtype of avian influenza (bird flu) has crossed the species barrier and causes severe illness in humans. Young are particularly affected. Oseltamivir is the antiviral of choice, and patients often need invasive ventilation. If H5N1 develops the ability to transmit efficiently between humans, an influenza pandemic is likely. SARS, belonging to the Coronaviridae family, was first seen in China in 2002, the outbreak finally contained in 2003; no treatments were conclusively effective. A species of hantavirus – 'Sin Nombre' virus – has a high mortality rate; rodents are the major host of hantaviruses.

CASE 1.5 LUNG CANCER

Instruction

This 67-year-old man has had a persistent cough. Please examine his respiratory system and discuss your findings.

Recognition

There may be one or a combination of clinical signs:

- *Cachexia*
- *Finger clubbing* (Fig. 1.13)
- *Chest signs* – consolidation, collapse or pleural effusion

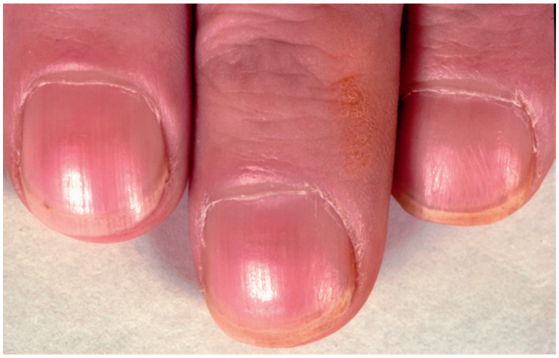


Figure 1.13 Finger clubbing.

- Cervical or supraclavicular *lymphadenopathy*
- *Horner's syndrome* +/− evidence of *brachial plexopathy* secondary to a Pancoast's tumour
- Signs of *superior vena cava obstruction* (SVCO).

Interpretation

Confirm the diagnosis

The differential diagnosis of lung cancer is wide:

- Slowly resolving pneumonia (consolidation)
- Lobar collapse by mucus plug
- Other causes of pleural effusion
- Benign tumour
- Metastases from an alternative primary site
- Lymphoma
- Pulmonary embolism
- Tuberculosis (TB) (weight loss, haemoptysis)
- Vasculitis (haemoptysis).

Management is directed at excluding serious and immediately threatening diagnoses (malignancy, pulmonary embolism, vasculitis, TB).

What to do next – assess other systems

Tell the examiners that you would ask about:

- *Endobronchial symptoms* (cough, dyspnoea, haemoptysis), *systemic symptoms* (weight loss, anorexia) and *pain* (e.g. infiltration of brachial plexus; metastatic bone pain)
- *Hormonal/metabolic symptoms* suggesting a paraneoplastic syndrome (Box 1.12).

Hypertrophic pulmonary osteoarthropathy is a very rare, extreme form of clubbing associated with wrist and ankle swelling and characterised radiologically by subperiosteal new bone separating from the cortex; it is most commonly associated with squamous cell carcinoma. A hoarse voice may represent recurrent laryngeal nerve palsy, and, although typically the result of lung cancer, other causes are sometimes the culprit, such as left atrial enlargement or an aortic arch aneurysm.

Box 1.12 **Lung cancer paraneoplastic syndromes**

- Parathyroid hormone-related peptide-induced hypercalcaemia, often the result of squamous cell carcinoma; hypercalcaemia is, however, mostly a consequence of bone metastases
- Ectopic secretion of numerous hormones including adrenocorticotrophic hormone (Cushing's syndrome) and antidiuretic hormone, commonly due to small-cell lung cancer, which is neuroendocrine derived
- Lambert–Eaton myasthenic syndrome

Table 1.6 World Health Organization / Zubrod performance status scale in lung cancer

Stage	Features
0	Asymptomatic
1	Symptomatic but ambulatory
2	In bed < 50% of day (unable to work but living at home with assistance)
3	In bed > 50% of day (unable to care for self)
4	Bedridden

Consider severity/decompensation/complications

Tell the examiners that you would look for signs of distant metastases, e.g. brain, bone, liver or skin.

Tell the examiners that persistent haemoptysis, stridor or signs of SVCO would warrant immediate referral to a chest physician.

Consider function

Performance status in lung cancer may be assessed by numerous scales, e.g. World Health Organization (WHO)/Zubrod (Table 1.6), Karnofsky.

Discussion

Is lung cancer incidence increasing?

It is globally the biggest cancer killer. The incidence is increasing in developing countries because of smoking.

What are the causes of lung cancer?

Smoking is implicated in 90% of cases. The risk is cumulative. Environmental/occupational exposure to asbestos, silicosis, arsenic, nickel, chromium, aromatic hydrocarbons and radon are rarer causes. The incidence is also increased in various medical disorders including idiopathic pulmonary fibrosis and dermatomyositis.

Which investigations would you consider when trying to establish a diagnosis of lung cancer?

An algorithm for lung cancer diagnosis is given in Figure 1.14.

What is the role of positron emission tomography (PET) scanning in lung cancer?

Computed tomography (CT) scanning has limitations. CT has poor sensitivity for detecting mediastinal nodes, especially < 1 cm in diameter, and many nodes < 1 cm in diameter are malignant whilst 40% of enlarged nodes on CT are benign. Some metastases are clinically silent and invisible on CT and so patients relapse after surgery. PET is a radionuclide technique that exploits the fact that tumour cells are metabolically more active and take up glucose more avidly than other cells. ^{18}F-labelled fludeoxyglucose (FDG) is an isotopically labelled glucose analogue-containing positron (proton)-emitting fluorine that is not cleared from tumour cells. FDG-PET is more sensitive and specific than CT in detecting metastases in nodes and distant organs and is very useful for assessing questionably large lymph nodes. PET combined with CT (PET-CT) is now the definitive staging technique, especially to rule out metastases if radical treatment is planned, although even PET cannot resolve nodules less than about 8 mm in diameter nor detect cerebral metastases. Further, PET-CT has a high false-positive rate of up to 40% and positive nodes on PET-CT require biopsy. Possible investigations to reduce the need for mediastinoscopy include endobronchial ultrasound and endoscopic ultrasound. These techniques may also be useful for non-lung cancer nodes such as in TB or sarcoid.

Other indications for PET are:

- CT inconclusive or negative when lung cancer is still suspected
- Bronchoscopy or biopsy inconclusive
- The patient is not fit for bronchoscopy or biopsy and CT is inconclusive (where diagnosis would make a difference).

PET is increasingly used in other cancers to identify if metastases are present and guide treatment decisions.

Why may earlier identification of lung cancer be important and how might this be achieved?

Early identification of lung cancer seems important because currently it is seldom diagnosed in stage 1, and 80% of cancers are inoperable at diagnosis. CT scanning is three times more sensitive than chest X-ray in detecting lung cancer. However, studies reveal that, although CT screening appears to enhance diagnosis of early lung cancer, there is no evidence that this reduces the likelihood of diagnosis of advanced lung cancer or the chance of dying from disease; indeed, such screening may be prone to overdiagnosis bias in which indolent lung cancers that would not have killed a patient in their own lifetime are diagnosed and treated with the concomitant risks of biopsy and thoracic surgery.

How is lung cancer classified?

About 20% is small-cell lung cancer (SCLC). About 80% is non-small-cell lung cancer (NSCLC) – squamous cell (primary disease often in the main bronchus), adenocarcinoma (often peripheral) or large cell.

How is NSCLC classified?

The TNM staging classification is used for NSCLC to produce subsets that help direct treatment (Table 1.7).

Staging of NSCLC is achieved as illustrated in Figure 1.15.

What is the impact of smoking cessation on lung cancer?

Smoking cessation reduces the rate of lung cancer: after 10 years of abstinence the risk being 30–50% of that in continuing smokers. Smoking is as addictive as heroin: 70% of smokers want to quit, 40% try annually and 10% remain abstinent at over 6 months; several attempts are therefore usually necessary. Varenciline has partial agonist activity blunting withdrawal and reducing craving and partial antagonist activity blunting the pleasure of nicotine; it appears to be more effective than buprenorphine or nicotine substitutes, but all agents should be packaged within a smoking cessation service.

What are the treatment options for NSCLC?

Surgery offers the best chance of cure and is considered for fit patients with early disease (Table 1.8). It may comprise lobectomy or pneumonectomy. Recurrence rates after segmentectomy are higher. Generally, FEV_1 should be > 1 litre to consider lobectomy and > 1.5 litres to consider pneumonectomy.

Radical radiotherapy, potentially curative, is indicated in patients with stage I, II or III NSCLC with a good performance status (WHO 0, 1). Fractionation regimens such as continuous hyperfractionated accelerated radiotherapy offer higher 2-year survival and are offered to patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy or patients with stage III NSCLC who cannot tolerate or who decline chemotherapy. Postoperative radiotherapy is not usually effective.

Chemotherapy is offered to patients with stage III or IV (distant metastases) NSCLC. Combinations of a platinum-based drug (carboplatin, cisplatin) with a third-generation drug (docetaxel, gemcitabine, paclitaxel, vinorelbine) control disease and improve survival and quality of life. Pemetrexed may be used for locally advanced and metastatic NSCLC. Biologics inhibiting epidermal growth

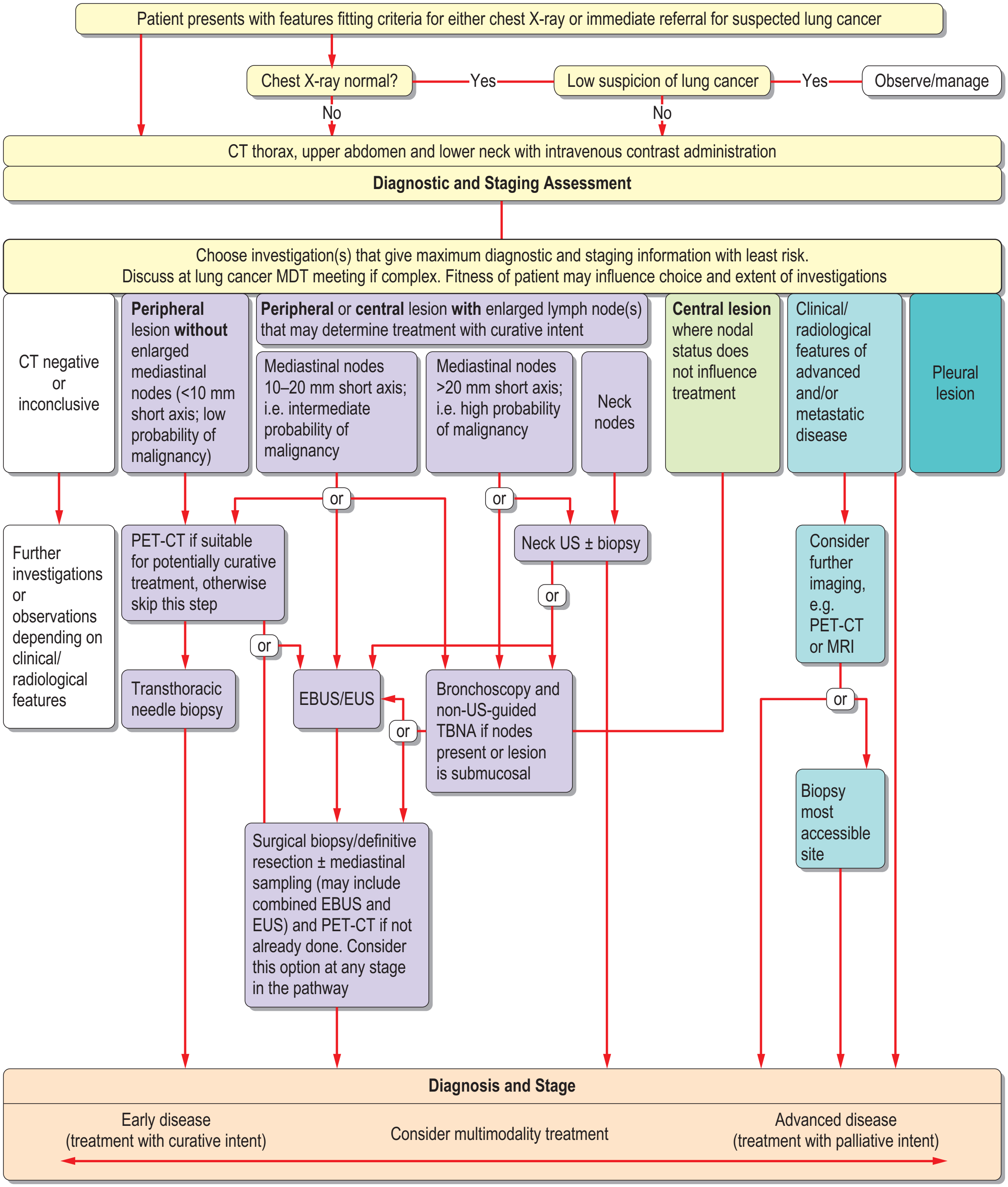

Patient presents with features fitting criteria for either chest X-ray or immediate referral for suspected lung cancer
Chest X-ray normal?
Yes
Low suspicion of lung cancer
Yes
Observe/manage
No
No
CT thorax, upper abdomen and lower neck with intravenous contrast administration
Diagnostic and Staging Assessment
Choose investigation(s) that give maximum diagnostic and staging information with least risk.
Discuss at lung cancer MDT meeting if complex. Fitness of patient may influence choice and extent of investigations
CT negative or inconclusive
Peripheral lesion without enlarged mediastinal nodes (<10 mm short axis; low probability of malignancy)
Peripheral or central lesion with enlarged lymph node(s) that may determine treatment with curative intent
Mediastinal nodes 10–20 mm short axis; i.e. intermediate probability of malignancy
Mediastinal nodes >20 mm short axis; i.e. high probability of malignancy
Neck nodes
Central lesion where nodal status does not influence treatment
Clinical/ radiological features of advanced and/or metastatic disease
Pleural lesion
or
or
Further investigations or observations depending on clinical/ radiological features
PET-CT if suitable for potentially curative treatment, otherwise skip this step
Neck US ± biopsy
or
Consider further imaging, e.g. PET-CT or MRI
or
Transthoracic needle biopsy
EBUS/EUS
or
Bronchoscopy and non-US-guided TBNA if nodes present or lesion is submucosal
or
Biopsy most accessible site
Surgical biopsy/definitive resection ± mediastinal sampling (may include combined EBUS and EUS) and PET-CT if not already done. Consider this option at any stage in the pathway
Diagnosis and Stage
Early disease (treatment with curative intent)
Consider multimodality treatment
Advanced disease (treatment with palliative intent)

Figure 1.14 Diagnosis of lung cancer. CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound; TBNA, transbronchial needle aspiration.

Table 1.7 Staging classification of non-small-cell lung cancer

		Tumour			
		T1	T2	T3	T4
		≤ 3 cm Lobar bronchus	> 3–7 cm Main bronchus > 2 cm to carina Invades visceral pleura	Any size < 2 cm to carina Invades chest wall, diaphragm, phrenic nerve, mediastinal pleura or parietal pericardium	Any size Invades other local structures, e.g. mediastinum, heart, oesophagus Malignant effusion
Nodes	N0	IA[a]	IB[a]	IIB[b]	IIIB[c]
	No nodes				
	N1	IIA[a]	IIB[a]	IIIA[b]	IIIB[c]
	Ipsilateral peribronchial, hilar or intrapulmonary nodes				
	N2	IIIA[b]	IIIA[b]	IIIA[c]	IIIB[c]
	Ipsilateral mediastinal or subcarinal nodes				
	N3	IIIB[c]	IIIB[c]	IIIB[c]	IIIB[c]
	Contralateral mediastinal or hilar nodes Any scalene or supraclavicular nodes				

[a] Offered surgery if fit. [b] Surgery may be suitable. [c] Surgery unsuitable.

Table 1.8 Staging and treatment of small-cell lung cancer

Stage	**Limited**	**Extensive**
(Defined by possibility of encompassing all detectable tumour within a 'tolerable' radiotherapy field)	Confined to one hemithorax Involves ipsilateral hilar nodes Involves ipsilateral and contralateral supraclavicular or mediastinal nodes With or without ipsilateral pleural effusion	Includes metastases in contralateral lung or distant metastases
Radiotherapy	Yes	No
Chemotherapy	Multidrug platinum-based regimen offered to all patients, response excellent but short-lived	
Surgery	Surgery has almost no role, micrometastatic spread invariable at diagnosis	

factor receptors and vascular endothelial growth factor receptors are emerging.

How is SCLC classified and treated?

CT of chest, liver and adrenals and additional selected imaging of symptomatic areas can determine whether disease is limited or extensive, and this helps to determine treatment (Table 1.8).

What palliative options are available in lung cancer?

These are outlined in Table 1.9.

What do you know about lung cancer prognosis?

Prognosis for both NSCLC and SCLC is poor, with only around one-third being potentially localised at presentation. In SCLC the median survival without treatment is 6 months for limited disease and 3 months for extensive disease, extended with treatment to 14–20 months for limited disease (5-year survival 10–20%) and 8–12 months for extensive disease (5-year survival 3–5%). For NSCLC, 5-year survival may be up to 60% for small tumours without nodal involvement, but drops rapidly for more extensive disease.

Table 1.9 Palliation of lung cancer symptoms

Symptom	Management
Breathlessness	Radiotherapy Debulking bronchoscopic procedures Endobronchial photodynamic therapy or brachytherapy Endobronchial stenting Pleural aspiration and pleurodesis
Cough / haemoptysis	Radiotherapy
Superior vena cava obstruction	Radiotherapy / chemotherapy Stenting
Brain metastases or spinal cord compression	Dexamethasone Radiotherapy
Bone metastases	Radiotherapy

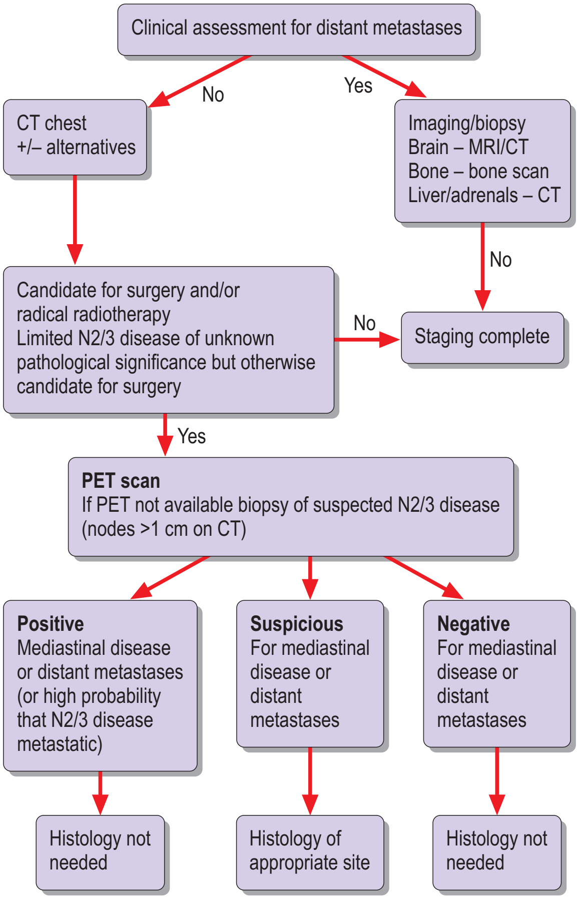

Clinical assessment for distant metastases
No
Yes
CT chest +/– alternatives
Imaging/biopsy
Brain – MRI/CT
Bone – bone scan
Liver/adrenals – CT
No
Candidate for surgery and/or radical radiotherapy
Limited N2/3 disease of unknown pathological significance but otherwise candidate for surgery
No
Staging complete
Yes
PET scan
If PET not available biopsy of suspected N2/3 disease (nodes >1 cm on CT)
Positive
Mediastinal disease or distant metastases (or high probability that N2/3 disease metastatic)
Suspicious
For mediastinal disease or distant metastases
Negative
For mediastinal disease or distant metastases
Histology not needed
Histology of appropriate site
Histology not needed

Figure 1.15 How non-small-cell lung cancer staging is achieved. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

CASE 1.6 PANCOAST'S SYNDROME

Instruction

This patient cannot abduct his shoulder. Please examine his respiratory system and discuss your findings.

Recognition

A tumour at the lung apex may invade locally to provoke Pancoast's syndrome (Fig. 1.16) with:

- Brachial plexus symptoms and signs, e.g. ipsilateral pain in the shoulder, upper anterior chest wall or between the scapulae, spreading to the arms and hands; unilateral *wasting of the intrinsic muscles of the hand*.
- An ipsilateral *Horner's syndrome* (small pupil, ptosis, absence of sweating).

Interpretation

Confirm the diagnosis

Signs of apical consolidation and a chest X-ray confirm the apical tumour.

What to do next – assess other systems

See Case 1.5.

Consider severity / decompensation / complications

See Case 1.5.

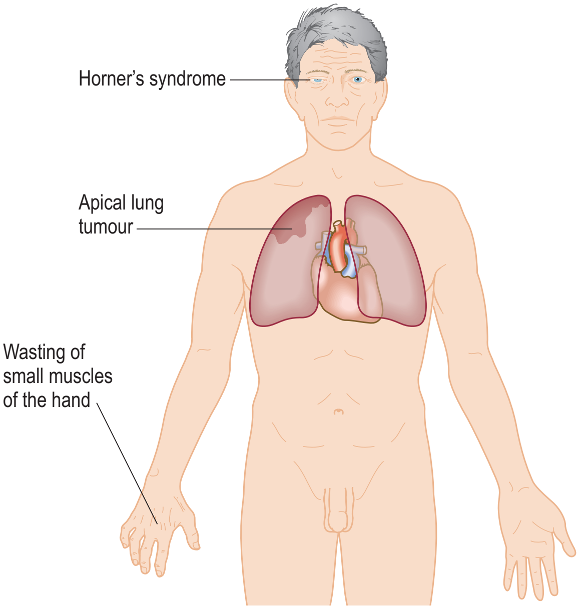

Horner's syndrome
Apical lung tumour
Wasting of small muscles of the hand

Figure 1.16 Pancoast's syndrome.

Consider function

See Case 1.5.

Discussion

How are Pancoast's tumours treated?

The three considerations are radiotherapy, chemotherapy and palliation.

CASE 1.7 SUPERIOR VENA CAVA OBSTRUCTION

Instruction

This elderly woman has been progressively breathless over the last few weeks. Please examine her hands, mouth, neck and chest and report your findings.

Recognition

There is *marked venous distension in the neck* (Fig. 1.17) and the jugular venous pulse is *raised and fixed*. There is also *distension of veins* in the *hands*, on the underside of the *tongue* and on the *chest wall* (Fig. 1.18).

Interpretation

Confirm the diagnosis

A chest X-ray may confirm a bulky mediastinum.

What to do next – assess other systems

See Case 1.5.

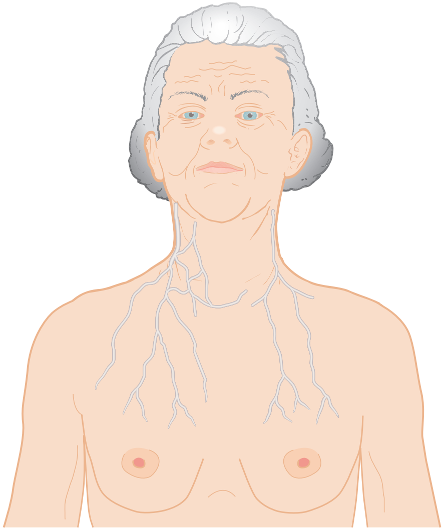


Figure 1.17 Superior vena cava obstruction.

Consider severity / decompensation / complications

See Case 1.5. As well as causing distension of veins of the upper torso and face plus swelling, SVCO can cause:

- Dyspnoea
- Chest discomfort
- Headaches
- Syncope (on bending)
- Laryngeal oedema.

Consider function

See Case 1.5.

Discussion

List some causes of superior vena cava obstruction (SVCO)

- Lymphoma
- Aortic aneurysm
- Mediastinal mass
- Mediastinal fibrosis

How is SVCO managed?

Tissue diagnosis rather than immediate steroid treatment is usually possible. The exception is with laryngeal oedema, which poses anaesthetic difficulties. Radiotherapy, chemotherapy or stenting may be considered to alleviate symptoms.

What are the main causes of an anterior mediastinal mass?

- Thymoma
- Thyroid goitre
- Lymphoma
- Teratoma
- Lymph node spread from carcinoma

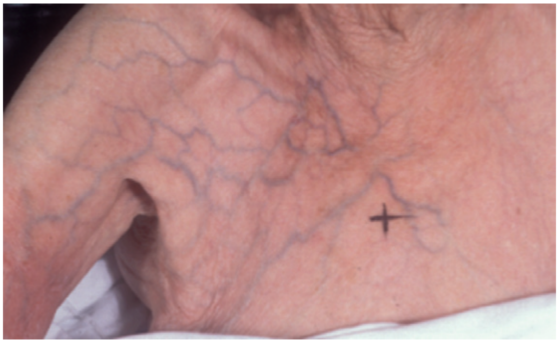


Figure 1.18 Dilated chest veins in superior vena cava obstruction.

CASE 1.8 COLLAPSE / PNEUMONECTOMY / LOBECTOMY

Instruction

This patient is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There is *tracheal deviation* (to the affected side). *Decreased chest expansion, dullness to percussion* and *decreased breath sounds* occur *on the affected side* (Fig. 1.19). There may be a thoracotomy scar (Fig. 1.20) indicating previous lobectomy / pneumonectomy.

Interpretation

Confirm the diagnosis

Consolidation causes dullness to percussion, bronchial breath sounds and increased vocal resonance; it may coexist with collapse.

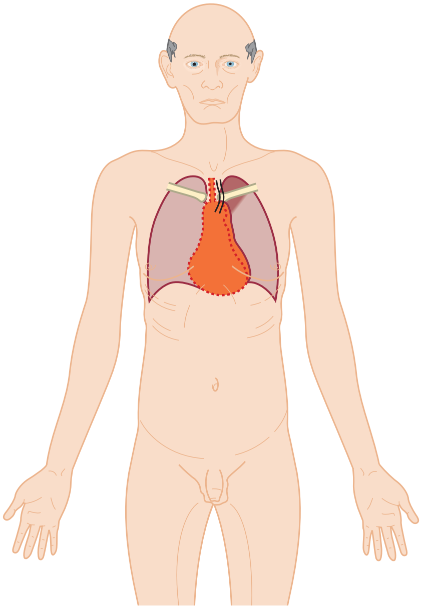


Figure 1.19 Lobar collapse.

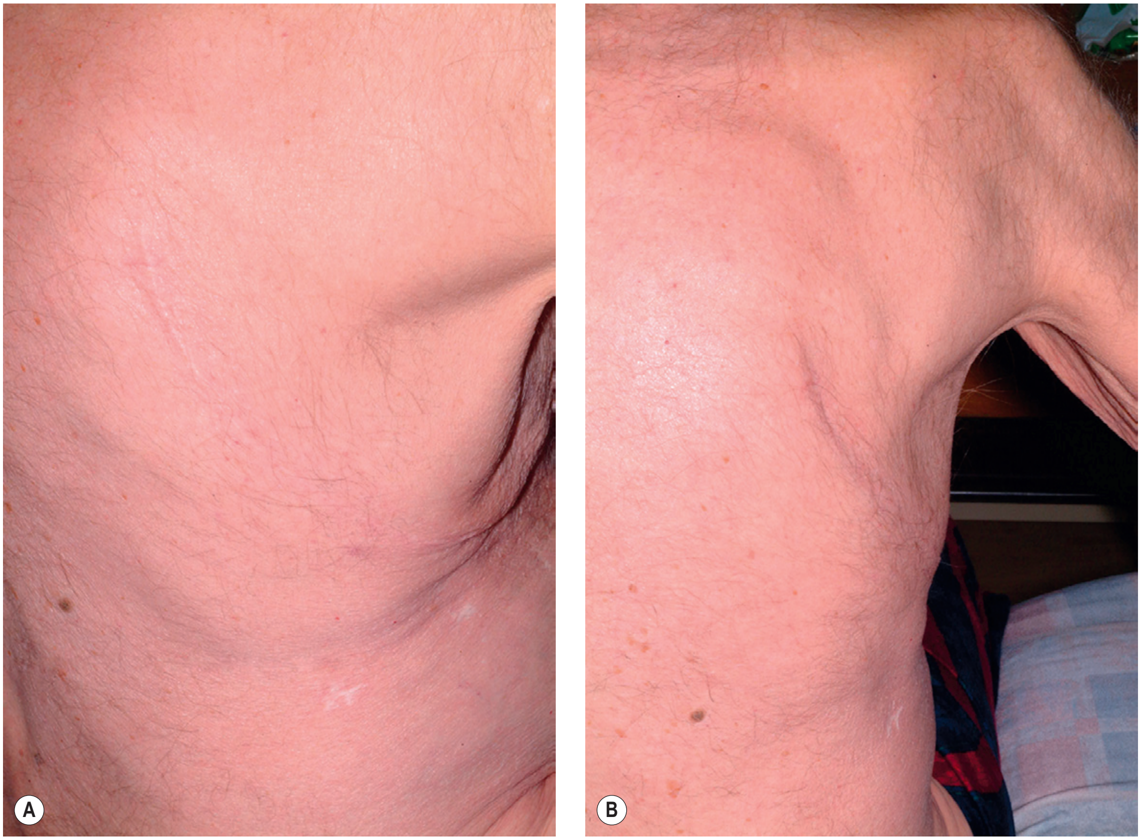


Figure 1.20 Thoracotomy scar.

What to do next – consider causes

Collapse is commonly due to pneumonia or lung cancer. Common reasons for previous lobectomy / pneumonectomy are lung cancer, tuberculosis (TB), localised bronchiectasis or bullae.

Consider severity / decompensation / complications

This depends on the underlying cause, e.g. pneumonia (CURB score), lung cancer (operability). Obstruction causing collapse may predispose to pneumonia or segmental bronchiectasis.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

List some causes of bronchial obstruction that can lead to collapse

- Carcinoma of bronchus
- Extrinsic compression, e.g. mediastinal lymph nodes
- Benign tumour
- Mucus plugs, e.g. asthma
- Foreign body
- Granulomata, e.g. TB, sarcoid

CASE 1.9 BRONCHIECTASIS

Instruction

This young man has been troubled by recurrent chest infections. Please examine his respiratory system and discuss possible causes.

Recognition

There is a *large volume* of *sputum* in the sputum pot beside the bed in this *underweight*, *dyspnoeic* and *cyanosed* patient with finger *clubbing*. Auscultation reveals *coarse*, *late inspiratory crackles* +/− inspiratory clicks (audible with the unaided ear) and wheeze (mucus obstructing distal airways) (Fig. 1.21).

Interpretation

Confirm the diagnosis

The differential diagnosis of clubbing and crackles includes idiopathic pulmonary fibrosis. Bronchiectasis should be considered in all adults who have persistent productive cough. Tell the examiners that the following support a diagnosis of bronchiectasis, any one of which warrants investigation:

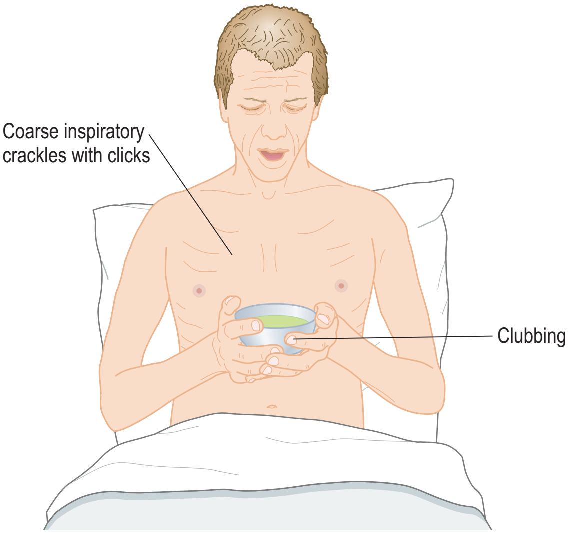


Figure 1.21 Bronchiectasis.

- Young age at presentation
- Chronic respiratory symptoms since early life or over many years
- Absence of or low smoking history
- Daily expectoration of large volumes of mucopurulent or purulent sputum
- Haemoptysis (minor haemoptysis is common in infective exacerbations, usually settling with antibiotic treatment)
- Sputum colonisation with *Pseudomonas aeruginosa*.

What to do next – consider causes

Tell the examiners that you would consider the causes of bronchiectasis (Box 1.13).

Consider severity / decompensation / complications

Consider the following complications:

- Cor pulmonale
- Bronchiectasis is a common cause of moderate or life-threatening haemoptysis; 90% of haemoptyses are from abnormal arteries in the bronchial circulation and bleeding is directly into airways – death is more likely from asphyxiation not exsanguination
- Empyema / abscesses
- Secondary amyloidosis.

Consider function

Tell the examiners you would establish the limitations caused by symptoms. The sputum has a hugely adverse impact on quality of life.

Box 1.13 **Causes of bronchiectasis**

- Idiopathic (around 50%)
- Postinfectious (up to 30%) – previous severe lower respiratory tract infections due to bacterial and viral pneumonia, pertussis or tuberculosis (mycobacterium tuberculosis and opportunist mycobacteria)
- Immunodeficiency (8%) – typically X-linked hypogammaglobulinaemia, immunoglobulin A deficiency, low levels of immunoglobulin G subclass 2 promoting recurrent infection with encapsulated bacteria
- Allergic bronchopulmonary apergillosis (7%) – asthma commonly associated
- Aspiration / inhalation of foreign body (6%)
- Autoimmune connective tissue disease (rheumatoid arthritis most commonly) (3%)
- Cystic fibrosis (2%)
- Disorders of ciliary function (< 1%) – primary ciliary dyskinesia or Kartagener's syndrome
- Ulcerative colitis (< 1%)
- The possibility of diffuse panbronchiolitis should be considered in patients of Far Eastern ethnic origin

Approximately 50% of people with chronic obstructive pulmonary disease (COPD) have some degree of bronchiectasis, detectable on high-resolution computed tomography. It is often localised, and it is unclear if COPD is the cause or if there are triggers for dual pathology. Traction bronchiectasis is common in fibrotic lung conditions.

Localised / segmental bronchiectasis suggests bronchial obstruction.

Discussion

What is bronchiectasis?

Bronchiectasis refers to irreversible, abnormal dilatation of one or more bronchi, with chronic airway inflammation, associated chronic cough and sputum production, recurrent chest infections, and air-flow obstruction. The pathogenesis is not known. Abnormal immune regulation may predispose to bronchiectasis both at the time of an initial insult that triggers disease and during the ongoing inflammatory process that ends in progressive lung damage. Progressive lung damage might occur as a result of the vicious cycle of inflammation and infection. There is a genetic susceptibility association with HLA-DR1, DQ5.

Which pathogens are common in bronchiectasis?

These include *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Pseudomonas aeruginosa* (uncommon in chronic obstructive pulmonary disease), *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, Gram-negative bacteria, non-tuberculosis mycobacteria and *Aspergillus* spp. Sputum should always be sent for culture.

What blood tests should be performed?

Serum immunoglobulins (IgG, IgA, IgM), serum electrophoresis, and testing for *Aspergillus* should be performed in all patients. Second-line assessment of immune competence should be considered if antibody screening demonstrates an antibody deficiency disorder or in the presence of normal antibody screening with clinical suspicion of immune deficiency, a family history of known or suspected immune deficiency or where infections are serious.

What criteria are used to diagnose allergic bronchopulmonary apergillosis (ABPA) in the setting of bronchiectasis?

ABPA is a clinical diagnosis based on presentation and immunological tests (*Aspergillus fumigatus*-specific IgE and IgG). There may be a history of asthma (spirometry), peripheral blood eosinophilia and increased total IgE.

When should patients have investigations to exclude cystic fibrosis (CF)?

All up to the age of 40 presenting with bronchiectasis should have investigations for CF. In adults, investigations should also be considered in those over 40 and no other identified cause, those with persistent isolation of *Staphylococcus aureus* in sputum, those with features of malabsorption, male primary infertility, upper lobe bronchiectasis, or a history of childhood steatorrhoea. Screening should include two measurements of sweat chloride and gene analysis.

When should patients have tests of ciliary function?

This should be considered if there is a history of chronic upper respiratory tract problems or otitis media, especially if there have been problems since childhood, there is predominantly middle lobe bronchiectasis, or there is infertility or dextrocardia.

What is the role of radiology in bronciectasis?

A chest X-ray is relatively insensitive but may show 'tramline' shadows indicating dilated, thickened bronchial walls. Ring shadows of end-on airways and fluid levels may also be present. Gross cystic or varicose bronchiectasis is now less common though occasionally seen after childhood pneumonia such as with bad measles. Diagnosis is clinical but confirmed by high-resolution computed tomography (HRCT). Three key features are:

1. Bronchial wall dilatation ('signet ring' appearances with an end-on bronchiole larger than the accompanying pulmonary artery)
2. Peripheral airways being visible < 1 cm from the lung margin
3. Lack of tapering of thickened bronchi ('tramlines').

Bronchial wall thickening and mucus plugging – 'flames and blobs' (mucus plugging of dilated bronchi) or nodular and V- or Y-shaped opacities (thickening and plugging of small airways) – are also common. HRCT may also suggest underlying conditions.

Which other tests should be considered?

Sputum culture should always be performed as well as blood tests. All adults should have spirometry. In adults with localised disease, bronchoscopy may be indicated to exclude proximal obstruction.

What are the principles of management in bronchiectasis?

These are outlined in Box 1.14.

Who should be referred to a chest physician?

- Those with difficult pathogens (e.g. *Pseudomonas aeruginosa*, meticillin-resistant *Staphylococcus aureus*)
- Those responding poorly to treatment (poor response to antibiotics, rapid relapse, frequent exacerbations)
- Younger patients
- Poor prognostic group patients (rheumatoid arthritis, ciliary problems, respiratory failure)

Box 1.14 **Management principles in bronchiectasis**

These include general approaches and treatment of a specific underlying cause:

- Physiotherapy techniques and exercises are used to assist airway clearance (postural drainage, active cycle breathing technique, oscillating positive expiratory pressure devices).
- Adjuncts to airway clearance include nebulised saline to increase sputum yield, reduce sputum viscosity and improve ease of expectoration.
- Antibiotics are used for exacerbations or prevention of exacerbations (patients having three or more exacerbations per year requiring antibiotic therapy or patients with fewer exacerbations that are causing significant morbidity should be considered for long-term nebulised antibiotics); higher doses and longer courses (e.g. 14 days) are recommended.
- Bronchodilators seem appropriate where lung function or symptoms improve with these.
- Non-invasive ventilation is used to augment tidal volume and reduce the work of breathing in those becoming fatigued.
- Bronchial artery embolisation is first-line therapy (before surgery, bronchoscopic tamponade or topical epinephrine (adrenaline) or tranexamic acid) for massive haemoptysis; the critical care, surgical and radiology team should be involved immediately and intubation, single-lung ventilation and bronchoscopy with suction are immediate measures.
- Lung resection surgery may be considered in patients with localised disease in whom symptoms are not controlled by medical treatment.
- Pulmonary rehabilitation exercises are used.
- Non-invasive ventilation can improve quality of life in some patients with chronic respiratory failure due to bronchiectasis.
- Airway pharmacotherapy (mucolytics and hyperosmolar agents, e.g. recombinant DNAase) and corticosteroids appear not be useful in bronchiectasis.

CASE 1.10 CYSTIC FIBROSIS

Instruction

This young man has recurrent chest infections. Please examine his respiratory system and discuss your findings.

Recognition

There is a *large volume* of *sputum* in the sputum pot beside the bed in this *underweight*, *dyspnoeic* and *cyanosed* patient with finger *clubbing*. Auscultation reveals *coarse, late inspiratory crackles* ± inspiratory clicks (audible with the unaided ear) and wheeze (mucus obstructing distal airways).

Interpretation

Confirm the diagnosis

Tell the examiners you wonder if cystic fibrosis transmembrane regulator (CFTR) gene testing has been performed.

What to do next – assess other systems

Tell the examiners you would ask about symptoms (Table 1.10).

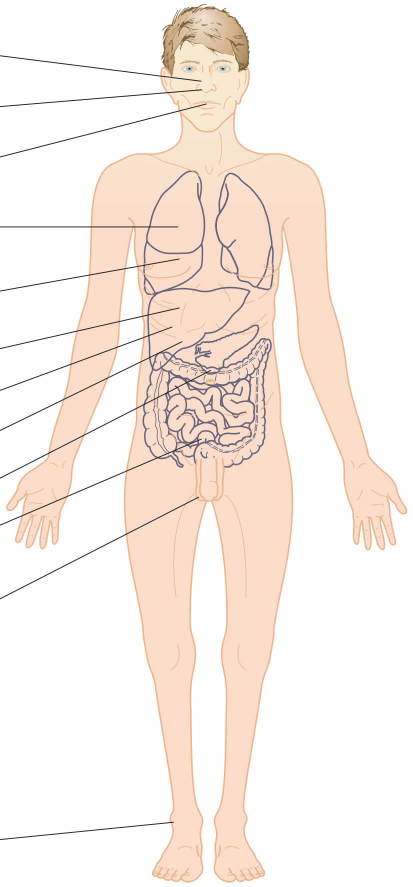
Consider severity / decompensation / complications

Tell the examiners that:

- Infection is inevitable – *Staphylococcus aureus* tends to affect infants, *Haemophilus influenzae* and *Klebsiella pneumoniae* appear through childhood, and *Pseudomonas aeruginosa* is ultimately almost inevitable. Chronic *Staphylococcus aureus* and *Pseudomonas aeruginosa* colonisation are almost impossible to eradicate. *Burkholderia* (*Pseudomonas*) *cepacia* infection can cause rapid decline; allergic bronchopulmonary aspergillosis (ABPA) and tuberculosis (TB) are also more common in cystic fibrosi (CF).
- Pneumothoraces, cor pulmonale and respiratory failure are common.
- Malabsorption leads to steatorrhoea and osteoporosis.
- A baby born with CF might now be expected to live past their fortieth birthday such that diabetes, biliary cirrhosis and arthropathies are more likely.

Table 1.10 Cystic fibrosis symptoms

System	Problems
Respiratory	Chronic sinusitis Nasal polyps Thick sputum, chronic cough, wheeze Recurrent infection – pneumonia, bronchitis, chronic low-grade infection with periodic relapses Bronchiectasis Pneumothoraces or severe haemoptysis (late stages)
Intestinal	Chronic liver disease Biliary cirrhosis Gallstones Pancreatic failure with malabsorption Intussusception and distal intestinal obstruction
Infertility	Male infertility due to failure of development or obstruction of the vas deferens and seminiferous tubules Female subfertility due to altered cervical mucus and menstrual irregularity
Arthropathy	Multiple joints



Consider function

The psychological and social consequences of CF are often overlooked, but huge. Teenagers find that CF interferes with friendships and school, adults may find work challenging, and low self-esteem is common.

Discussion

Discuss the pathophysiology of cystic fibrosis (CF)

CF is autosomal recessive with a gene carriage rate of around one in 20 in Caucasians and a disease incidence of around one in 2000. Most CF is due to a mutation in chromosome 7 at position 508 where the codon for phenylalanine is deleted, although many mutations in the same gene have been described. The result is that the CFTR protein, a cAMP regulated channel for chloride, is not produced in its normal form. CFTR normally permits chloride efflux from the luminal surface of airway epithelial cells; some sodium influx parallels this. In CF, chloride fails to escape but that this is associated, strangely, with excess sodium influx. It is thought that this may seduce water from the lumen, resulting in viscous secretions, the water level at the surface being critical to mucus secretion. CF is pathophysiologically a complex disease because affected epithelial surfaces have different actions in their native state – airways and intestinal epithelial surfaces are volume absorbing, sweat ducts salt absorbing and the pancreas volume secreting – causing diverse clinical sequelae.

How is CF diagnosed?

It often starts with clinical suspicion in a child with unknown carrier parents. Chronic productive cough, poorly responsive 'asthma', chronic sinusitis, nasal polyps, chronic diarrhoea or failure to gain weight may raise suspicion. A sweat sodium concentration > 60 mmol/l is traditional, but modern techniques may allow detection

Table 1.11 Treatments for cystic fibrosis (CF)

Treatment	Comments
Physiotherapy	Daily chest percussion and physiotherapy with postural drainage reduces respiratory exacerbations
Antibiotics	Early high-dose, broad-spectrum, long-duration (minimum 2–3 weeks) antibiotics minimise lung damage in infective exacerbations Oral or intravenous fluoroquinolones (intravenous preferred for exacerbations in chronically infected patients), combined with nebulised antibiotic often the initial choice; resistance and chronic carriage needs intravenous combinations CF nurses can administer therapy at home Specialist antibiotics for less common organisms, mycobacterial infection or allergic bronchopulmonary apergillosis Prophylactic antibiotics increasingly used
Bronchodilators	Symptomatic relief
DNase mucolytics administered as an aerosol spray	Interferes with sputum neutrophil DNA, helping to liquefy sputum and encourage expectoration, reducing cough
Pancreatic enzyme replacement	Helps avoid malabsorption
Immunisation	Routine pneumococcal and influenza vaccination
Lung transplantation	Considered if pulmonary function < 30% with chronically infected, purulent bronchiectasis Side effects of immunosuppression significant ≥ 70% of patients survive > 1 year and 50% > 5 years
Palliative care	Advanced CF

of the voltage across airway cells produced by chloride and sodium; this is normally –20 mV, but in CF may be around 50 mV. Genetic testing is now also used.

What are the treatment options for CF?

These are outlined in Table 1.11.

Does gene therapy offer the potential for cure?

This has great potential in the next few years. CFTR nebulised alone into the airway is ineffective because it is unable to get into the epithelium. Thus two options are viral or liposomal (fat globule) carriage of CFTR. Viral carriage has the advantage of 200–300 million years of evolution, and Sendai virus carriage has been shown to cure CF; unfortunately this cure lasts for about a week as gene expression falls rapidly, and 'infection' cannot be repeated as the effect wanes rapidly as viral immunity develops. Thus, a non-viral approach seems mandatory. Importantly, CF carriers with 50% of CFTR have no lung disease, and indeed patients with congenital absence of vas deferens who have very little CFTR do not have lung disease. Thus a little CFTR, if capable of being delivered and retained, gives a lot, the likely requirement being 5% of CFTR mRNA in only 5% of cells to 'cure' CF. There are hundreds of potential gene transfer agents, but only a small number are non-toxic and give reproducible results and one lysosome, lipid 67, has already worked in sheep. Results are inconsistent, but the stage is set for industry product development – current treatment would be prohibitively costly at a few million pounds per patient per year. The other limiting factor is a clinical trial, the cost of a sample size of a few hundred patients needed to power it prohibitive, and the question arises as to what would be an appropriate outcome measure in such a trial.

CASE 1.11 KARTAGENER'S SYNDROME

Instruction

This patient has a frequent productive cough and breathlessness. Please examine his respiratory system and discuss your findings.

Recognition

There is a *large volume* of *sputum* in the sputum pot beside the bed in this *underweight*, *dyspnoeic* and *cyanosed* patient with finger *clubbing*. Auscultation reveals *coarse*, *late inspiratory crackles* ± inspiratory clicks (audible with the unaided ear). The *apex beat* is on the *right*.

Interpretation

Confirm the diagnosis

The combination of bronchiectasis and dextrocardia suggests Kartagener's syndrome (Box 1.15).

Box 1.15 Kartagener's syndrome

- Bronchiectasis (ciliary dysmotility)
- Dextrocardia
- Situs invertus
- Infertility
- Frontal sinus dysplasia
- Sinusitis
- Otitis media

What to do next – assess other systems

Tell the examiners that you would ask about sinus problems and fertility.

Consider severity / decompensation / complications

Look for signs of cor pulmonale.

Consider function

Tell the examiners you would establish the limitations caused by symptoms.

Discussion

List some more common causes of bronchiectasis

- Cystic fibrosis
- Postinfective (pneumonia, tuberculosis, measles, whooping cough)
- Allergic bronchopulmonary apergillosis
- Hypogammaglobulinaemia
- Localised bronchiectasis secondary to bronchial obstruction

CASE 1.12 TUBERCULOSIS

Instruction

Please examine this patient's chest and comment on your findings.

Recognition

Whilst the incidence of active tuberculosis (TB) is rising, you may still see the legacy of surgical treatments for TB. The broad aims were to render affected lung hypoxic (to kill the organism) and to close cavities. The results of these aims may include:

- *Thoracotomy scarring* posteriorly / previous rib resections. There is *chest deformity*. The *trachea deviates to the same side*, where there is *decreased expansion* and *breath sounds are reduced*.
- Scarring from iatrogenic pneumothoraces.
- *Supraclavicular fossae scarring* indicating previous phrenic nerve crush procedures. Again, there may be *diminished chest expansion*.

Interpretation

Confirm the diagnosis

Former TB may also be suggested by apical flattening and upper lobe crackles from fibrosis. Thoracoplasty was a common treatment for TB before the days of antimicrobial therapy. This may be associated with a 'white-out' of lung collapse on the chest radiograph. Pneumothoraces may leave calcified or thickened pleura radiologically. A raised hemidiaphragm may be seen radiologically in patients who underwent phrenic nerve crush.

What to do next – assess other systems

Tell the examiners that TB may be pulmonary or extrapulmonary. Extrapulmonary manifestations, in approximate order of frequency, are listed in Table 1.12. TB is a resurgent disease in cities of Western Europe, with an increased proportion of extrapulmonary disease.

Consider severity / decompensation / complications

List some complications to the examiners. Note that acute respiratory distress syndrome (ARDS) is a rare, acute, life-threatening complication of TB.

Consider function

Tell the examiners that the social situation is vital from a public-health perspective.

Discussion

What is happening to the prevalence of tuberculosis (TB)?

Mycobacterium tuberculosis is increasing in prevalence worldwide, infecting previously healthy and immunosuppressed (human immunodeficiency virus (HIV)-infected relative risk 100, with annual risk of TB acquisition 10%) individuals with increasingly multidrug-resistant strains. Globally it is the world's biggest infectious disease killer, infecting 2 billion people and killing 1.7 million people per year. In the UK, 70% of TB affects ethnic minority groups, and most TB in white people occurs in middle-aged to elderly patients. Migration, socioeconomic deprivation, HIV co-infection and the greater use of immunosuppressive agents and biological therapies have all contributed to the increasing prevalence. The impact of diabetes on TB prevalence, well recognised decades ago but in recent decades underappreciated, is substantial and an awareness renaissance is expected.

Table 1.12 Extrapulmonary tuberculosis (TB)

Region		Clinical features	Usual mode of spread
Pleural		Effusion Empyema (rare)	Direct
Lymph node (tuberculous lymphadenitis)		Painless lymphadenopathy (cervical or supraclavicular)	Direct
Pericardial		Pericarditis Pericardial effusion Tamponade	Direct
Genitourinary		Haematuria Dysuria Flank pain Pelvic pain Infertility	Haematogenous
Skeletal		Osteomyelitis Septic arthritis	Haematogenous
Gastrointestinal		Terminal ileum / caecum (abdominal pain, diarrhoea) Fever, weight loss, night sweats	Swallowing of sputum Haematogenous
Miliary (disseminated small 'millet seed' deposits in lungs and other organs)	3 forms: acute, cryptic chronic, 'non-reactive' (caseation in many organs)	Fever, weight loss, night sweats, symptoms related to region involved Cryptic miliary TB often presents in older people with weight loss and a normal chest X-ray and can be rather covert	Haematogenous
Meningeal		Meningitis	Haematogenous
Less common	Eyes	Chorioretinitis Uveitis Painful hypersensitivity phlyctenular conjunctivitis (grey nodules near the limbus)	Haematogenous
	ENT	Simulation of Wegener's granulomatosis	Direct Haematogenous
	Skin	Erythema nodosum Erythema induratum Scrofularosum / abscesses Lupus vulgaris Chronic ulcers	Direct inoculation Haematogenous
	Adrenals	Hypoadrenalism	Haematogenous

What different stages of TB may occur?

These are shown in Figure 1.22. Infection with TB following exposure relates predominantly to duration of exposure, and to some extent proximity.

Latent TB infection (LTBI)

Infection is occasionally transient, but the vast majority will develop LTBI – the *Mycobacterium tuberculosis* (MTB) complex usually resists clearance and can remain in an apparently clinically inactive state for many years before symptomatic disease develops, if ever; almost one-third of the world's population are thought to have LTBI.

Active TB – primary TB

A small proportion will develop active TB and in those in whom TB does develop it usually occurs within 2 years of initial infection, termed primary TB.

The first active infection with the tubercle bacillus is termed primary TB and is usually respiratory TB. *Mycobacterium tuberculosis* can remain airborne for minutes to hours after people with pulmonary or laryngeal TB cough. The primary infection site is usually subpleural, occasionally tonsillar or ileocaecal. Bacteria are taken up by alveolar macrophages, leading to a cascade of events resulting in *containment* or progression – *primary progressive TB*. After macrophage ingestion, *Mycobacterium tuberculosis* replicates slowly but continuously at the primary site and spreads via the lymphatics to regional, often hilar, lymph nodes. In most people, vigorous pro-inflammatory immunity develops within 2–8 weeks. The primary infection site and regional lymph nodes are termed the primary complex, where macrophages and activated T lymphocytes form granulomata that aim to limit further replication and spread. *Mycobacterium tuberculosis* inhabits the centre of these characteristically necrotic (caseating or cheese-like) granulomata, and is usually not viable. Unless there is a defect in cell-mediated immunity, infection should remain contained and active disease may never occur. Thus, the primary complex may result in one or more of numerous potential outcomes (Table 1.13).

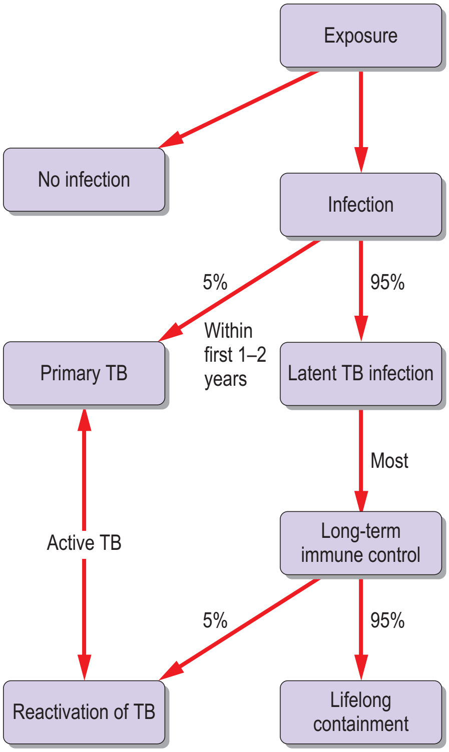


Figure 1.22 Stages of tuberculosis (TB).

Active TB – reactivation

Those with LTBI usually progress to long-term immune control and long-term containment (it is very common, for example, for respiratory physicians to be in this state) whilst a few will experience reactivation, the second type of active TB; progression to active disease at this stage may occur naturally, but is frequently precipitated by states of debilitation or immunosuppression. There may be direct progression or haematogenous spread (Fig. 1.23), often with fever, anorexia, weight loss or night sweats. The incubation period for TB may thus be from weeks to a lifetime!

Why does TB tend to affect the upper lobes?

These are the most highly oxygenated, sustaining the organism.

What is meant by tuberculin sensitivity?

After 2–8 weeks, sensitisation to tuberculin protein develops owing to the cell-mediated immune response. TB provokes a heavy T-helper 1 lymphocyte-mediated pro-inflammatory response. At the cellular level, infected macrophages release interleukins 12 and 18, which stimulate T-helper 1 lymphocytes (CD4) to release interferon-γ, which in turn stimulates macrophage phagocytosis. CD8 and indeed the full spectrum of T cells are involved in the immune response.

How is TB diagnosed?

By definition, MTB cannot be cultured from an individual with LTBI, so diagnosis relies on detecting a host immune response to the organism. Further, most effort is spent on early detection of pulmonary (hence infectious) TB, but almost half of UK cases are extrapulmonary. Inflammatory markers such as C-reactive protein should logically be positive, but are not always so.

Table 1.13 Four potential outcomes of primary pulmonary tuberculosis (TB)

Outcome		**What happens**
Long-term immune control or containment	Asymptomatic infection	Discovered as incidental X-ray finding (90% of primary TB heals, with calcification, leaving its legacy, the Ghon focus, as spread is arrested)
	Local symptoms	Persistent cough or compression of bronchus by primary complex
	Overt cell-mediated immune response	Fever Erythema nodosum Phlyctenular conjunctivitis
Primary progressive TB or reactivation of TB (direct progression or haematogenous spread)		Replication cannot be contained Common in children and immunosuppressed Pulmonary or extrapulmonary features (Table 1.12)

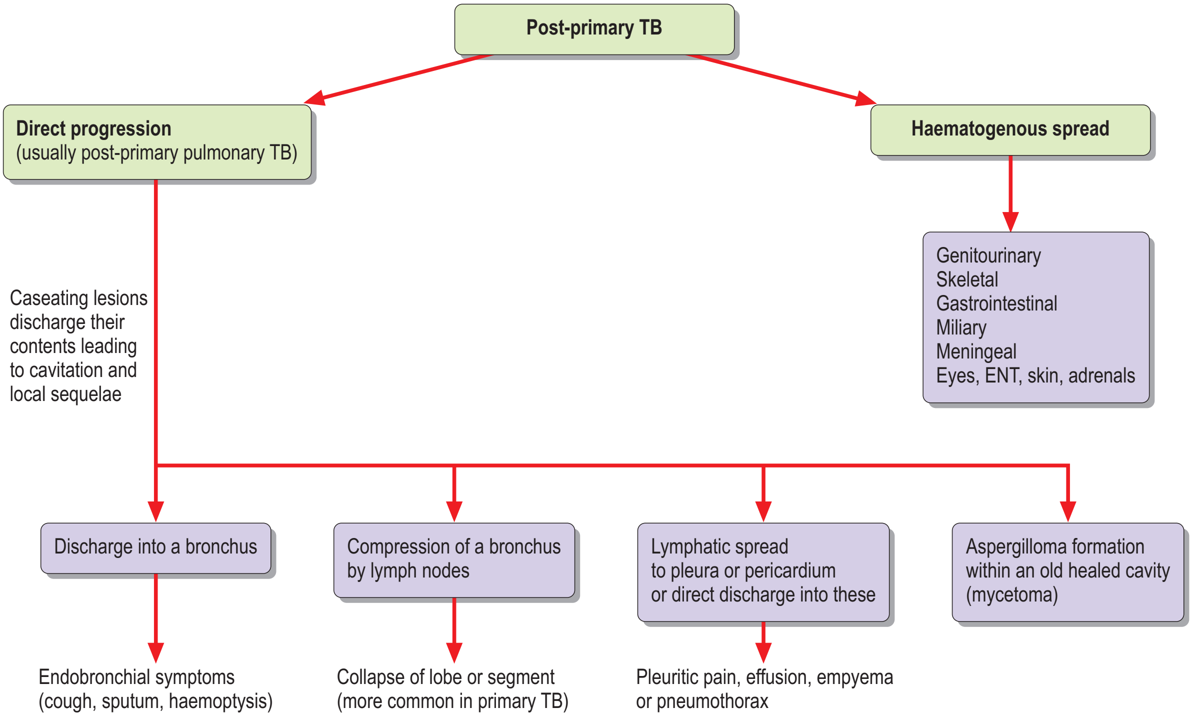

Post-primary TB
Direct progression (usually post-primary pulmonary TB)
Haematogenous spread
Genitourinary
Skeletal
Gastrointestinal
Miliary
Meningeal
Eyes, ENT, skin, adrenals
Caseating lesions discharge their contents leading to cavitation and local sequelae
Discharge into a bronchus
Compression of a bronchus by lymph nodes
Lymphatic spread to pleura or pericardium or direct discharge into these
Aspergilloma formation within an old healed cavity (mycetoma)
Endobronchial symptoms (cough, sputum, haemoptysis)
Collapse of lobe or segment (more common in primary TB)
Pleuritic pain, effusion, empyema or pneumothorax

Figure 1.23 Post-primary tuberculosis (TB).

Tuberculin skin tests

Tuberculin sensitivity gives rise to the positive tuberculin skin test (TST). The Mantoux test is the commonest TST, using intradermal purified protein derivative in the volar aspect of the forearm; induration diameter is measured at 72 hours and a diameter < 6 mm is negative and > 10 mm positive for past or present TB (> 15 mm if previous bacillus Calmette–Guérin or BCG vaccination). The problem with TSTs is that sensitivity and specificity are very poor; false-negative TSTs occur particularly in immunocompromised people in whom cell-mediated immunity is impaired (anergy).

Chest radiography

Chest radiography may show patchy or nodular (usually bilateral upper lobe) opacification, calcification, volume loss or cavitation. Disease inactivity cannot be inferred from X-ray.

Microbiological isolation

Microbiological isolation of the acid-fast bacillus using either Ziehl–Neelsen or fluorescent stains confirms the diagnosis but in 50% of cases the bacterium is never isolated. Sputum is usually negative because bacilli in lesions tend not to communicate with bronchi. Morning gastric washings are sometimes helpful. Other options include pleural aspiration or biopsy, lymph node biopsy, bone marrow biopsy, bronchial lavage, early morning urine specimens or cerebrospinal fluid examination. Sputum, if necessary by lavage, is essential for diagnosing reactivated TB. All of this said, the gold standard TB test remains culture from a body fluid or tissue.

Modern diagnostic assays

In recent years, the interferon-γ (IFN-γ) release assay (IGRA) has been developed which detects the specific IFN-γ evoked by the strong T-helper type 1 (cell-mediated immune) response to MTB antigens (e.g. ESAT6 and CFP10) in host cells. IGRA tests utilise a variety of MTB antigens that are not present in BCG and are more specific than TSTs. They are also largely blood based and provide results within 24 hours. The availability of these assays raises the question of screening at-risk people such as those embarking on immunosuppression. The assays only confirm infection, not risk of progression to active TB.

Is BCG immunisation useful?

BCG is given intradermally and protection is still considered useful but under constant review. It is now administered only to those deemed at risk rather than through a national schools programme, e.g. occupational risk factors, infants in areas where incidence is over 40/100 000 or whose relatives were born in such an area, and previously unvaccinated immigrants from countries where prevalence is high. BCG is a live vaccine and should be avoided in immunosuppressed people. It can cause local abscess formation, regional lymphadenitis and keloid scarring.

Which individuals with TB should be targeted for treatment?

Those at high risk should be targeted; this includes those known to be within a year or two of infection who are at risk of primary TB, and those immunocompromised, especially with HIV.

Which drugs are used to treat TB?

For active TB a standard recommended regimen is isoniazid and rifampicin (HR) for 6 months with pyrizinamide and ethambutol during the first 2 months (HRZE). For active meningeal TB a 12-month regimen with glucocorticoid is used. Variations in the standard regimen, some including glucocorticoid, depend upon the site affected. The choice of regimen and monitoring should be provided by a chest physician, and the World Health Organization categorises the widening range of antituberculosis drugs, which include fluoroquinolones and second-line injectable agents such as streptromycin.

What do know about drug-resistant TB?

Drug resistant TB is becoming more common and may be classified into the categories in Box 1.16. Risk factors include a history of TB treatment, contact with a person with drug-resistant TB, HIV infection, male sex, being age 25–44 years, being born outside the UK or residing in London.

Traditional laboratory methods for detecting resistance are slow. Rapid molecular methods are increasingly used and a microscopic observation drug susceptibility (MODS) assay is possible. The evidence base to guide drug treatment of resistant TB is weak.

Box 1.16 **Drug-resistant tuberculosis (TB)**

- *Drug-resistant TB* – TB resistant to any first-line antituberculosis drug
- *Multidrug-resistant TB* – TB resistant to at least isoniazid and rifampicin
- *Extensively drug-resistant TB (XDR-TB)* – TB resistant to at least isoniazid and rifampicin and also to a fluoroquinolone and second-line injectable agent
- *Drug resistance in new TB cases (primary drug resistance)* – drug-resistant TB in a person with no history of TB treatment, implying infection with a resistant organism. This reflects person-to-person transmission of drug-resistant TB
- *Drug resistance among previously treated cases ('acquired' drug resistance)* – drug-resistant TB in a person with a history of TB treatment. This reflects drug resistance acquired during TB treatment or infection or reinfection with a resistant organism

CASE 1.13 IDIOPATHIC PULMONARY FIBROSIS AND INTERSTITIAL LUNG DISEASE

Instruction

This 60-year-old man has been increasingly short of breath on exertion. Please examine his hands and chest and discuss your findings.

Recognition

There may be *finger clubbing* (50% of patients with idiopathic pulmonary fibrosis (IPF) and may accompany other interstitial lung diseases (ILDs)). There are *bilateral, fine, late inspiratory* ('*Velcro*') *crackles at the lung bases*, which do not clear with coughing.

Interpretation

Confirm the diagnosis

Bilateral, fine, late inspiratory crackles characterise ILD and if basal IPF is a common possible cause. Bronchiectasis crackles are coarser, and earlier in inspiration. Left ventricular failure crackles may be less 'crackly'.

What to do next – consider causes

There are many types of ILD. Tell the examiners you would ask about symptoms suggesting as possible cause (Box 1.17).

History is key! Tell the examiners that you would take a history for drugs, environmental exposure to dusts, and connective tissue disease. Smoking is associated with several ILDs but some forms, such as hypersensitivity pneumonitis and sarcoidosis, are less common in smokers. Although familial clustering is well described in sarcoidosis, familial ILD is rare.

Box 1.17 **Symptoms of interstitial lung disease (ILD) that suggest a possible cause**

- Cough, breathlessness with reduced exercise tolerance, and crackles – usually insidious and progressive – characterise ILD.
- Wheeze is not a feature except in pulmonary eosinophilia associated with asthma.
- Haemoptysis occurs in pulmonary haemorrhage and vasculitis.
- Large sputum volumes suggest bronchiectasis.
- Chest pain is rare except in systemic lupus erythematosus.
- Pneumothorax is common in the rare cystic interstitial lung diseases.
- Pleural effusion is occasional in connective tissue lung diseases.
- Fever suggests infection, vasculitis or malignancy rather than ILD.
- Weight loss suggests malignancy but can occur in any severe ILD.

Box 1.18 **Examples of drugs that can cause interstitial lung disease**

- Antibiotics, e.g. cephalosporins, minocycline, nitrofurantoin*, quinine
- Rheumatology drugs, e.g. non-steroidal anti-inflammatory drugs, methotrexate, gold, leflunomide, penicillamine, sulphasalazine, biologics
- Cardiac drugs, e.g. amiodarone, angiotensin-converting enzyme inhibitors, aspirin, atenolol, statins
- Oncology drugs, e.g. bleomycin, busulfan, chlorambucil, melphalan, methotrexate, mitomycin C, tyrosine kinase inhibitors (dasatnib, imatinib)
- Immunomodulators, e.g. methotrexate, azathioprine, cyclophosphamide, rapamycin derivatives (sirolimus), epidermal growth factor receptor inhibitors (gefitinib, erlotinib), interferons, tumour necrosis factor-α blockers, rituximab
- Miscellaneous, e.g. high-flow oxygen, inhalation or aspiration of fat-containing substances, paraquat*, radiotherapy, illicit drugs (cocaine, heroin, methadone)

*Nitrofurantoin, captopril and paraquat ‘steal electrons’ and produce oxidative stress.

Drugs

Examples of drugs that can cause ILD are in Box 1.18.

Environmental exposure – dusts

Hobbies, occupation, travel and other possible environmental exposures should be considered:

- Inorganic dusts linked with ILD include asbestos, coal, silica and beryllium. New industries have generated new forms of ILD, e.g. flockworker’s lung in manufacturers of synthetic microfibres (flock) and metalworker’s lung in those exposed to metalworking aerosols. Gases such as chlorine also cause ILD.
- Hypersensitivity pneumonitis can be caused by antigens in organic dusts, such as thermophilic actinomycetes including *Saccharopolyspora rectivirgula* in hay causing farmer’s lung, and proteins in bird droppings and on feathers causing bird or pigeon fancier’s lung. Other causes include feathers in duvets, domestic mould exposure, *Mycobacterium avium* complex in hot-tub lung and *Trichoderma koningii* in woodworker’s lung.

Connective tissue disease

Any connective tissue disease may be complicated by ILD. Occasionally pulmonary symptoms predate rheumatological. Note especially any signs of connective tissue disease in the skin, eyes and joints, e.g. scleroderma (Fig. 1.24), malar rash, facial telangictasia, uveitis, joint swelling. ILD is particularly common in rheumatoid arthritis, e.g. 50% have a degree of non-specific interstitial pneumonitis (NSIP)-like change on high-resolution computed tomography (HRCT) but this is of little significance, whilst ILD in scleroderma is much more severe.

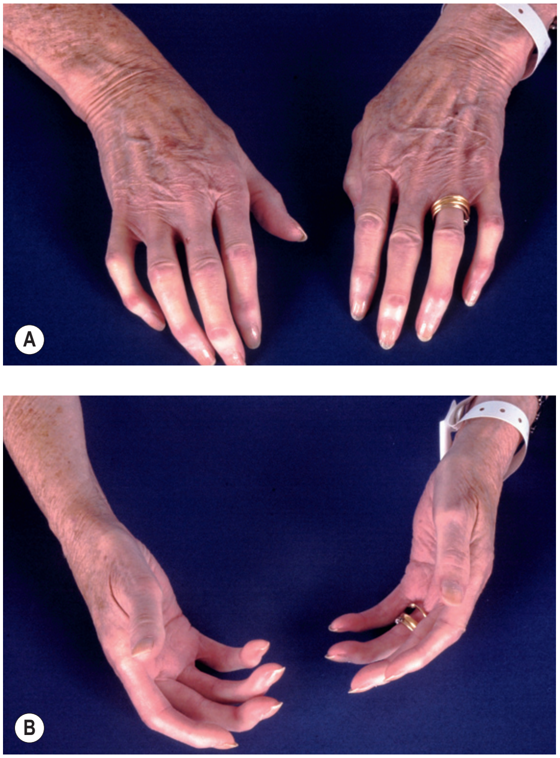


Figure 1.24 (A and B) Scleroderma.

Consider severity / decompensation / complications

Tell the examiners that:

- Crackles become more widespread and may extend into expiration as disease progresses
- Pulmonary hypertension may complicate almost any ILD, but is particularly common in systemic sclerosis
- In any advanced disease there may be hypoxia, central cyanosis and signs of cor pulmonale, again particularly common in systemic sclerosis.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

What do you understand by the term interstitial lung disease (ILD)?

The interstitium refers to the narrow space between the alveolar epithelium and capillary endothelium, crucial for gas exchange (Fig. 1.25).

ILD refers to a heterogenous group of over 200 diseases in which the intersitium becomes thickened, often with alveolar transudates or exudates; the term diffuse parenchymal lung disease (DPLD) includes alveolar filling diseases but most DPLD is synonymous with ILD. The common final pathway for many ILDs is fibrosis and some forms are life threatening, such as IPF, formerly known as cryptogenic fibrosing alveolitis.

Why is ILD important?

ILD is important because it is:

1. Common (there are around 4000 new cases in England and Wales of IPF and 3000 new cases of sarcoidosis in the UK each year)
2. Lethal (IPF survival rates are 57% at 3 years and 43% at 5 years, with a median survival of around 36 months)
3. Preventable and treatable in many cases.

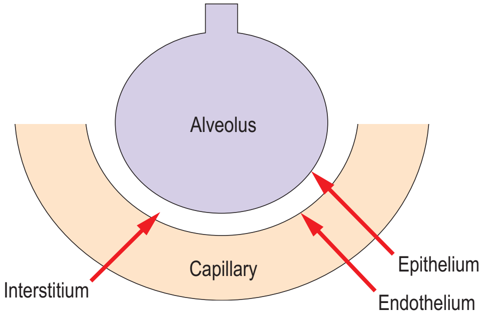


Figure 1.25 The pulmonary interstitium.

How is ILD classified?

ILD classification remains a little messy. It has been classified by the British Thoracic Society according to time course (Table 1.14).

The current histopathological classification of ILD is summarised in Figure 1.26.

The most common causes of ILD are IPF, sarcoidosis, connective tissue diseases and dusts.

Idiopathic interstitial pneumonias

This term refers to a group of seven related ILDs, the most common of which is IPF, which has a particularly poor prognosis. Idiopathic interstitial pneumonias are classified by the British Thoracic Society into seven histological subtypes with differing appearances on HRCT and different prognostic implications (Table 1.15). These are IPF, whose histological correlate is usual interstitial pneumonitis (UIP), and six types of non-IPF idiopathic interstitial pneumonia. UIP is by far the commonest (6–14 per 100 000), followed by NSIP. UIP has a dismal prognosis compared with all others, which may respond to steroids and other treatments.

Table 1.14 Classification of interstitial lung disease (ILD) by time course

Time		Examples
Acute (< 3 weeks)		Hypersensitivity pneumonitis Infection Acute interstitial pneumonia Toxin Pulmonary haemorrhage or vasculitis, e.g. Wegener's granulomatosis, Goodpasture's syndrome, idiopathic pulmonary haemosiderosis
Episodic		Eosinophilic pneumonia Cryptogenic organising pneumonia Vasculitis, e.g. Churg–Strauss syndrome
Chronic, secondary to:	Occupation (often termed pneumoconiosis if inorganic dust inhaled)	Asbestosis Silicosis Coal worker's pneumoconiosis
	Environmental agent (often termed hypersensitivity pneumonitis if occupational or recreational organic dust)	Farmer's lung Bird fancier's lung
	Drug	Many drugs causative but also patients with pre-existing ILD much more likely to develop severe disease
Chronic, secondary to systemic disease		Connective tissue disease, e.g. systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis Granulomatous, e.g. sarcodiosis Neurofibromatosis / tuberose sclerosis
Chronic – unknown cause		Idiopathic pulmonary fibrosis and most of the other idiopathic interstitial pneumonias

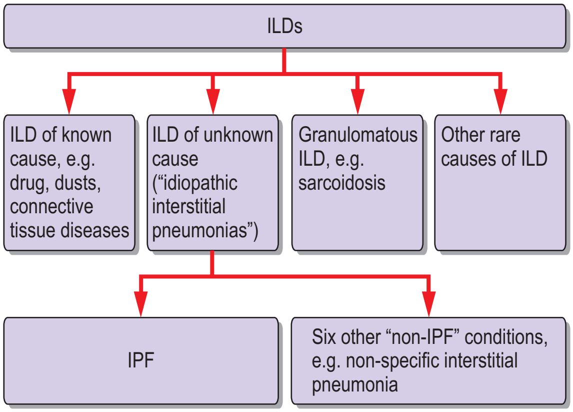

ILDs
ILD of known cause, e.g. drug, dusts, connective tissue diseases
ILD of unknown cause ("idiopathic interstitial pneumonias")
Granulomatous ILD, e.g. sarcoidosis
Other rare causes of ILD
IPF
Six other "non-IPF" conditions, e.g. non-specific interstitial pneumonia

Figure 1.26 Current classification of interstitial lung disease (ILD). IPF = idiopathic pulmonary fibrosis.

Mention some rare causes of ILD

Langerhans cell histiocytosis (LCH) and lymphangioleiomyomatosis (LAM) are nodular and cystic lung diseases; in LCH irregular cysts are distributed predominantly in upper and mid-zones and in LAM thin-walled cysts distributed evenly. The former is more common in young male smokers, characterised by excessive Langerhans cells, and may require corticosteroids. The latter is more common in young women, sometimes associated with tuberose sclerosis, characterised by smooth muscle cell proliferation and infiltration and causes irreversible damage without effective treatment. Alveolar proteinosis refers to the accumulation of protein-rich and lipid-rich material in alveoli and is sometimes associated with silica exposure or haematological disorders with immunodeficiency.

What is meant by the terms acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)?

ALI and ARDS are respiratory syndromes occuring following a wide variety of insults and are defined by:

- Acute onset (< 7 days)
- Bilateral pulmonary infiltrates on chest X-ray
- Pulmonary capillary wedge pressure < 18 mmHg or absence of left atrial hypertension cinically
- Hypoxaemia – p_aO_2/F_iO_2 ratio < 40 kPa in ALI and < 27 kPa in ARDS (for a p_aO_2 of 10 kPa and an F_iO_2 of 0.21 – 21% oxygen or room air – the p_aO_2/F_iO_2 ratio is 47.6).

ARDS shares similar features to sepsis but may be triggered by conditions other than sepsis, including trauma. The pathophysiology is incompletely understood. There is neutrophil recruitment to the lung, with alveolar and systemic release of chemokines (e.g. CXCL-8), pro-inflammatory cytokines and matrix-remodelling enzymes (e.g. MMP-9). Exaggerated neutrophil inflammation damages the alveolar–capillary barrier leading to non-cardiogenic pulmonary oedema, which may resolve early or lead rapidly to fibrosis, this substantially determining outcome. There is an increased prevalence of the DD ACE genotype in people with ARDS. Treatments in intensive care include treatment of cause, oxygen (including extracorporeal membrane oxygenation) and ventilatory support (e.g. high-frequency oscillatory ventilation), but there are no proven pharmacological strategies. Many controversies in management include oxygen levels (mortality rises with hypoxaemia though this is not the whole story as Everest mountain climbers can tolerate a p_aO_2 of 3.5 whilst those in intensive care with a p_aO_2 of 25 may be profoundly unwell, and hyperoxia is known to be dangerous and potentially fatal by damaging endothelium), mode of ventilation, fluid management, optimum haemoglobin concentration and use of drug therapies.

What first-line tests might you consider in suspected interstitial lung disease?

The following are important tests.

Chest radiograph

- The chest X-ray be normal in early ILD, but is usually abnormal once disease is clinically apparent. Abnormalities include decreased lung volumes, subpleural reticular or reticulonodular opacities, bilateral interstitial shadowing, peripheral migratory air space shadowing, and mediastinal or hilar lymph node enlargement. It may also help to identify a cause.
- The distribution of shadows may give clues (upper or mid-zones – hypersensitivity pneumonitis, ankylosing spondylitis, sarcoidosis, radiation fibrosis; lower zone – IPF, NSIP, drug or connective tissue disease-associated ILD, asbestosis). In IPF profuse crackles and a highly abnormal HRCT may be associated with an almost normal chest radiograph, although the chest X-ray is invariably abnormal in at least subtle ways. Conversely, in sarcoidosis, signs may be absent with widespread radiographic changes.
- Some conditions which can produce similar chest X-ray changes include pneumonia, pulmonary oedema, lymphangitic carcinomatosis, miliary tuberculosis, bronchiectasis and bronchoalveolar cell carcinoma.

Oximetry (at rest and ideally on exertion)

An oxygen saturation of less than 94% at rest is abnormal.

Spriometry

This can be deceptively normal.

Bloods

- A full blood count, including eosinophils, serum biochemistry profile (including renal and liver

Table 1.15 Idiopathic interstitial pneumonias

Histological classification	Histology	Potential causes	Features	High-resolution CT (HRCT)	Treatment	Prognosis
UIP	Heterogeneous features within the same field – normal lung alternating with interstitial inflammation and fibrosis with fibroblastic foci producing collagen	Unknown A repeated stimulus probably provokes sequential lung damage with aberrant wound healing and fibrosis IPF is strongly associated with smoking Possible environmental factors include metal and wood dusts in those genetically predisposed Chronic micro-reflux and infection are also postulated Possible genetic factors include a genetic variant of transforming growth factor-β	UIP is the histological correlate of IPF with major and minor diagnostic criteria Major criteria: 1. Exclusion of other causes 2. Typical pulmonary function 3. Typical HRCT 4. No alternative diagnosis on biopsy or bronchoalveolar lavage Minor criteria 1. > 50 years 2. Insidious 3. Present > 3 weeks 4. Bibasal inspiratory crackles	Bilateral, patchy, peripheral, basal, subpleural reticular changes – if severe progresses to traction bronchiectasis and honeycombing (ground-glass opacification less common, correlating with active inflammation and cellularity)	No treatment satisfactory Lung transplantation only cure and considered if young Steroids and immune suppression do not appear to work Possible treatments include *N*-acetylcysteine (converted to glutathione, a naturally occurring antioxidant), pirfenidone (an anti-fibrotic), tyrosine kinase inhibitors and anticoagulants	Relentlessly progressive Poor prognosis – mean survival 2–4 years (30–50% 5-year survival) Better prognosis if young, female, predominant ground-glass pattern on CT, improvement in first 6 months or smoker at diagnosis (unclear why)
NSIP	Uniform inflammation and fibrosis (identical pattern seen in connective tissue diseases, recovery phase of ARDS and sequalae to COP and some forms of hypersensitivity pneumonitis)	Viral Metal or wood dusts Autoimmune	Clinically indistinguishable from IPF Middle age with slight female preponderance	Bilateral, symmetrical, basal, subpleural changes – may be reticular Ground-glass opacification and consolidation, often linear	Corticosteroids +/– cyclophosphamide (scleroderma-related NSIP responds well) Consideration of oxygen therapy, treatment of pulmonary hypertension and lung transplantation	Better prognosis than UIP (70% 5-year survival) but worse than RB-AILD and DIP
COP – formerly known as bronchiolitis obliterans organising pneumonia	Buds of organising granulation tissue and inflammation in alveoli	Viral	Fifth and sixth decade preponderance Subacute (75% present with symptoms for < 2 months) breathlessness, cough, systemic symptoms and high ESR	Non-segmental, often bilateral and multifocal, sometimes flitting patchy airspace consolidation with ground-glass pattern	Rapid response to corticosteroids, 0.5–1 g/kg prednisolone o.d. gradually tapered over 6–12 months	May relapse
AIP or Hamman–Rich syndrome	Histologically identical to ARDS – diffuse alveolar damage and later fibrosis	Viral Autoimmune	Acute and rapidly progressive Usually previously healthy	Patchy ground-glass opacification and consolidation, tending to affect dependent areas	Poor response to steroids and immunosuppression	High mortality (> 50%)
RB-ILD	Macrophage infiltration around bronchioles	Cigarettes	Smokers Male–female ratio 2 : 1 Extension of the inflammatory bronchiolitis that is a usual feature of COPD	Patchy ground-glass opacification with thickening of central and peripheral airways and centrilobar nodules	Good response to smoking cessation Seldom needs steroids	Good
DIP	Like RB-ILD but alveoli affected	Cigarettes	Rare (< 3% this subtype) Younger smokers Male–female ratio 2 : 1 Insidious Clubbing in 50%	Widespread patchy ground-glass opacification with basal and peripheral predominance	Good response to smoking cessation Good response to steroids (70% 10-year survival)	Good
Lymphocytic interstitial pneumonia	Dense lymphoid infiltrate	Immunodeficiency Lymphoproliferative disease Autoimmune	Male–female ratio 1 : 5	Ground-glass opacification		

AIP, acute interstitial pneumonitis; ARDS, acute respiratory distress syndrome; COP, cryptogenic organising pneumonia; COPD, chronic obstructive pulmonary disease; DIP, desquamative interstitial pneumonia; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonitis; RB-AILD, respiratory bronchiolitis-associated interstitial lung disease; RB-ILD, respiratory bronchiolitis interstitial lung disease; UIP, usual interstitial pneumonia.

function tests, calcium, glucose, thyroid function, C-reactive protein), and arterial blood gas measurement are essential. Polycythaemia is rare despite hypoxia.

- If a connective tissue disease is suspected antinuclear antibody, extractable nuclear antigens, rheumatoid factor, and anti-neutrophil cytoplasmic antibody testing are needed. A high titre for rheumatoid factor or antinuclear antibody (> 1 : 160) suggests connective tissue disease but low titres are common in IPF.
- If an environmental factor is suspected, specific serum IgG antibody screens can be performed for antigens (e.g. *Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris, Aspergillus*).
- British Thoracic Society guidelines suggest that measuring serum angiotensin-converting enzyme (ACE) has a limited role in the diagnosis of suspected sarcoidosis – assays have limited sensitivity and specificity, values are affected by ACE gene polymorphisms and raised in many other conditions including other granulomatous diseases (leprosy, tuberculosis, histoplasmosis), and are invalidated by an ACE inhibitor.
- Testing for human immunodeficiency virus infection may be helpful, since some forms of ILD are associated, such as lymphocytic interstitial pneumonia.
- Brain natriuretic peptide, secreted in response to ventricular stretch by cardiomyocytes, is a marker of right ventricular dysfunction, and elevated levels might identify patients with pulmonary hypertension and poorer prognosis.

Electrocardiogram

This may show signs of associated heart disease, right ventricular strain secondary to lung disease, and rarely conduction defects in cardiac sarcoidosis.

What second line tests might you consider in suspected interstitial lung disease?

High-resolution computed tomography (HRCT)

HRCT is an imaging test in which thin (< 1.5 mm) axial sections of the lungs are acquired with 10 mm or 20 mm gaps between sections. No intravenous contrast is used. Image reconstruction with a high spatial frequency algorithm allows sub-millimetre structures to be visualised. HRCT is a comparatively low-dose test, with a radiation exposure six times less than that of a conventional thoracic CT, and equivalent to approximately 50 chest X-rays. It should be reserved for patients with clinical or radiographic suspicion of ILD. Indications for HRCT are:

- To detect ILD in patients with clinical or radiographic suspicion of ILD and to aid the differential diagnosis
- To evaluate disease reversibility
- To guide the type and site of lung biopsy.

Features of IPF on HRCT are summarised in Table 1.15. The main value of HRCT is the identification of ILD and the most common variant, IPF. An appropriate clinical context and the presence of classic HRCT features allow a confident non-invasive diagnosis without lung biopsy. Ground-glass opacity is often present in IPF and in the absence of adjacent fibrosis is associated with response to treatment and longer survival. Patients with features of fibrosis at diagnosis (including honeycombing and reticular change) have a worse prognosis and the extent of lung fibrosis is a predictor of death.

Detailed pulmonary function tests (PFTs)

PFTs offer useful baseline and monitoring information.

- Diseases of lung parenchyma, including ILDs, typically have a ‘restrictive’ pattern on spirometry – forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are both reduced, resulting in a preserved or sometimes increased FEV_1 : FVC ratio. But this is not always the case, particularly in smokers, who may have coexisting emphysema and normal or near normal lung volumes resulting from the opposing effects of hyperinflation and fibrosis. Other ILDs associated with relative preservation of lung volumes include respiratory bronchiolitis-associated ILD, Langerhans cell histiocytosis and lymphangioleiomyomatosis. In IPF a fall in FVC of > 10% is clinically important, associated with a 2.4-fold increase in mortality.
- Transfer factor (also known as diffusing capacity for carbon monoxide) allows non-invasive assessment of gas exchange and is typically reduced in ILD; spuriously raised transfer factor can occasionally result from pulmonary haemorrhage in vasculitis or anaemia in the context of ILD. A disproportionately reduced transfer factor with relatively normal spirometry may suggest a vascular rather than interstitial lung disease process including pulmonary hypertension.
- Exercise tests (e.g. 6-minute walk) may help evaluate disease severity. Some patients are well at rest but profoundly hypoxic when walking. Exercise-associated oxygen desaturation significantly correlates with pulmonary hypertension and is useful prognostically.

Lung biopsy

If key radiological features are present the diagnostic accuracy of HRCT approaches 90–100% and surgical lung biopsy under general anaesthetic is unnecessary. Furthermore, biopsy in late honeycomb disease often only demonstrates fibrosis. Biopsies are most helpful with uncertain diagnosis. The site of surgical biopsy is best informed by HRCT. Video-assisted thoracoscopic surgery (VATS) is now routine, rather than open thoracotomy. Biopsy is taken from at least two lobes and the biopsy with the pathological pattern associated with the poorest prognosis should dictate treatment and estimate prognosis. Fibreoptic bronchoscopy, under local anaesthetic, allows visualisation of proximal airways and sampling of more distal lung using transbronchial biopsy, and bronchoalveolar lavage to exclude infectious causes. It is particularly useful in sarcoidosis, cancer, acute pulmonary eosinophilia, cryptogenic organising pneumonia, subacute hypersensitivity pneumonitis, and some rarer ILDs such as alveolar proteinosis.

Bronchoaleolar lavage (BAL)

BAL may be useful when infection is considered. Predominant neutrophils suggest IPF, NSIP or acute interstitial pneumonitis. Predominant lymphocytes suggest hypersensitivity pneumonitis, sarcoidosis or cryptogenic organising pneumonia. Inclusion particles may be seen in pneumoconioses (e.g. asbestos bodies confirm asbestos exposure). A foamy appearance may occur in hypersensitivity pneumonitis and drug-induced ILD. Lipoproteinaceous material occurs in alveolar proteinosis. Intracellular bodies are seen on electron microscopy in Langerhans cell histiocytosis. Haemosiderin-containing macrophages suggest pulmonary haemorrhage.

Echocardiography

Pulmonary hypertension should be considered in patients with ILD who have either breathlessness or lung dysfunction (reduced transfer factor or desaturation on exercise). Pulmonary hypertension is defined as a mean pulmonary artery pressure of greater than 25 mmHg at rest, or 35 mmHg or greater during exercise, with normal left atrial pressure. Right heart catheterisation is the gold standard test, but invasive. The prevalence of pulmonary hypertension varies widely according to disease and severity, but is relatively high (30–40%). Levels of pulmonary hypertension correlate with mortality.

What eosinophilic lung diseases do you know of?

Eosinophils are predominantly tissue leucocytes, differentiating in bone marrow under the influence of interleukins 5 and 3 and granulocyte–macrophage colony-stimulating factor and seduced to tissues from blood by chemokines, including eotaxins. Eosinophilic disorders occur when excess eosinophils release toxic granular contents, prostaglandins and platelet-activating factor and stimulate mast cell degranulation leading to vascular permeability changes, mucus production and smooth muscle contraction. Eosinophilic lung diseases are outlined in Table 1.16. Some other lung diseases are sometimes accompanied by eosinophilia, e.g. sarcoidosis, IPF, lung cancer, lymphoma.

Table 1.16 Eosinophilic lung diseases

Category	Diseases	Descriptions
Atopy	Asthma	Eosinophilia modest ($< 1.5 \times 10^9$ / l)
	Allergic bronchopulmonary aspergillosis	Common, usually in people with asthma or chronic lung disease Caused by a ubiquitous fungus (also causes aspergilloma in cavities and invasive aspergillosis in the immunocompromised) Inhaled spores cause eosinophilic bronchial and alveolar inflammation with breathlessness Chest X-ray infiltrates are dynamic (change over days or weeks) Blood eosinophilia, positive skin test for *Aspergillus fumigatus*, immunoglobulin G and E antibodies to *A. fumigatus*, precipitating antibodies to *A. fumigatus* (e.g. to metabolic or somatic antigen) and high total immunoglobulin E Treated with long-term or intermittent corticosteroids and sometimes systemic antifungals Tends to improve, but may progress to chronic fibrotic lung disease
Infection	Helminths and parasites	Eosinophilia usually modest
Drugs	e.g. nitrofurantoin, NSAIDs, antibiotics, sulfasalazine, methotrexate	
Idiopathic	Simple pulmonary eosinophilia (Loeffler's syndrome)	Eosinophilia modest ($< 1.5 \times 10^9$ / l) Transient bilateral infiltrates and few symptoms Resolves without treatment
	Eosinophilic pneumonias (chronic more common than acute)	Insidious cough, breathlessness, fever, weight loss Respiratory failure possible More common in middle-aged women 50% have asthma 80% have peripheral blood eosinophilia Peripheral patchy consolidation in upper and mid-zones on chest X-ray + / – cavitation Treated with long-term corticosteroids

Continued

Table 1.16 Eosinophilic lung diseases—cont'd

Category	Diseases	Descriptions
	Idiopathic hypereosinophilic syndrome	Rare (may be due to a gene deletion activating tyrosine kinase) Eosinophilia > 1.5×10^9 / l; may be very high Lungs and heart affected, e.g. heart failure
	Churg–Strauss syndrome	Established asthma Eosinophilia > 1.5×10^9 / l; may be very high Flitting or dynamic pulmonary infiltrates Multisystem, usually ANCA-associated, small vessel vasculitis, e.g. upper respiratory tract, skin, peripheral nerves, gastrointestinal, cardiovascular, renal

ANCA, anti-neutrophil cytoplasmic antibody; NSAIDs, non-steroidal anti-inflammatory drugs.

CASE 1.14 RHEUMATOID LUNG

Instruction

This patient is breathless. Please examine her respiratory system and discuss your findings.

Recognition

There are *fine crackles* in *both lungs* in this patient with *rheumatoid arthritis* and *rheumatoid nodules* (Fig. 1.27).

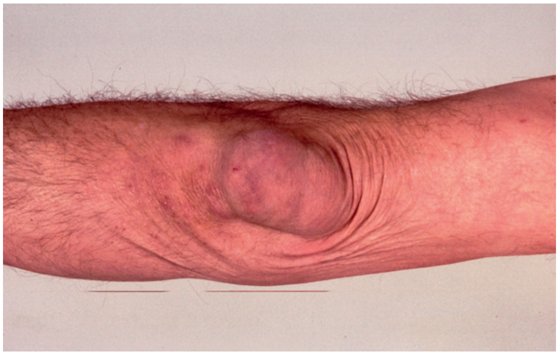


Figure 1.27 Rheumatoid nodule.

Interpretation

Confirm the diagnosis

Rheumatoid hands and nodules strongly suggest rheumatoid lung.

What to' do next – assess other systems

Tell the examiners that rheumatoid nodules are associated with many other extra-articular manifestations of rheumatoid arthritis (Case 5.11).

Consider severity / decompensation / complications

Rheumatoid lung fibrosis does not usually cause respiratory failure.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

List some lung manifestations of rheumatoid arthritis

- Pleuritic pain
- Pleural effusions
- Pulmonary fibrosis
- Pulmonary nodules
- Methotrexate-induced fibrosis or nodules
- Caplan's syndrome

CASE 1.15 HYPERSENSITIVITY PNEUMONITIS (EXTRINSIC ALLERGIC ALVEOLITIS)

Instruction

This patient is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There may be *clubbing* (in fibrotic types). There are *inspiratory crackles* and *high-pitched squeaks* or squawks (often) in the *mid-zones*.

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about occupation and hobbies.

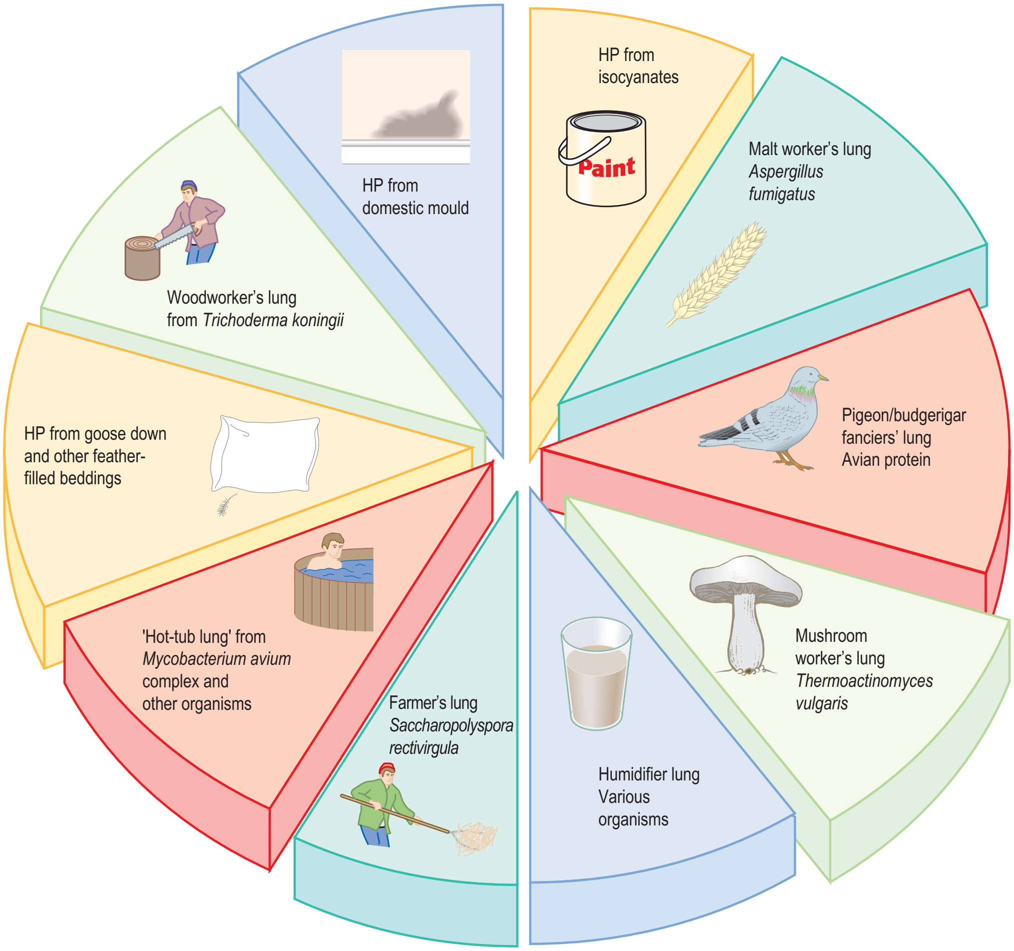

HP from domestic mould
HP from isocyanates
Paint
Malt worker's lung *Aspergillus fumigatus*
Woodworker's lung from *Trichoderma koningii*
Pigeon/budgerigar fanciers' lung Avian protein
HP from goose down and other feather-filled beddings
'Hot-tub lung' from *Mycobacterium avium* complex and other organisms
Farmer's lung *Saccharopolyspora rectivirgula*
Mushroom worker's lung *Thermoactinomyces vulgaris*
Humidifier lung Various organisms

Figure 1.28 Causes of hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis (EAA).

What to do next – consider causes

Hypersensitivity pneumonitis, otherwise known as extrinsic allergic alveolitis, refers to a group of diseases triggered by hypersensitivity to inhaled organic dusts and animal proteins. A vast array of types of hypersensitivity pneumonitis has been described including the ones illustrated, almost invariably organic (Fig. 1.28). Goose down and other feather-filled beddings are now common causes, and increasingly recognised are domestic mould exposure, *Mycobacterium avium* complex in 'hot-tub lung' and *Trichoderma koningii* in woodworker's lung.

Consider severity / decompensation / complications

Hypersensitivity pneumonitis can cause type 1 respiratory failure.

Consider function

Tell the examiners you would explore the impact of symptoms on work and of work on symptoms.

Discussion

What are the patterns of disease in hypersensitivity pneumonitis?

There are two clinical patterns (Table 1.17). Acute hypersensitivity pneumonitis is a flitting phenomenon that follows exposure by a few hours, worsening with ongoing exposure. It is typically worse at the end of the day and produces a sensation of choking or being unable to inspire; cough and fever may be present and signs may be minimal. Diagnosis in acute hypersensitivity pneumonitis may rely on a chest X-ray, pulmonary fucntion tests

Table 1.17 Acute and chronic hypersensitivity pneumonitis

	Acute	Chronic
Immune response	Early (within hours of high-concentration exposure) Immune complex (type III hypersensitivity) + T-cell-mediated acute alveolitis	Prolonged exposure Delayed cell-mediated chronic alveolitis (type IV hypersensitivity)
Pathology	Alveolar inflammation – early neutrophils and later lymphocytes on bronchoalveolar lavage Non-caseating granulomata	Chronic inflammation
Symptoms	Cough, breathlessness, fever, myalgia	Exertional breathlessness
Signs	Inspiratory crackles Hypoxia	Inspiratory crackles and squeaks Clubbing rarely
Blood tests	Neutrophilia May be immunoglobulin precipitins (present in some asymptomatic farmers and bird-keepers)	Appropriate precipitins in 90%
Chest X-ray	Small (1–3 mm) nodules in lower zones or diffuse infiltrates	Upper and mid-zone fibrosis
Pulmonary function tests	Restrictive defect (occasionally mixed restrictive / obstructive) Reduced lung volumes Reduced gas transfer	Restrictive defect (occasionally mixed restrictive / obstructive) Reduced lung volumes Reduced gas transfer
High-resolution CT	Diffuse ground-glass opacification Ill-defined centrilobar nodules and mosaic pattern Ill-defined nodules Patchy ground-glass shadows	Fibrosis, with reticular change, traction bronchiectasis and occasional honeycombing Lower zones often predominant in contrast to chest X-ray
Progress	Settles within a few days May progress if antigen is not removed	Poorly reversible
Treatment	Not needed	Trial of steroids

(showing a restricitve inspiratory pattern) and high-resolution computed tomography scanning soon after exposure. Symptoms melt with oral steroids within hours (unlike asthma, which can take a day or two), but otherwise, in the absence of exposure, take a few days to disappear. Episodes of acute hypersensitivity pneumonitis in people for whom identifiaction and removal of the allergen does not occur may lead to chronic hypersensitivity pneumonitis, a condition that can become self-perpetuating. Hypersensitivity pneumonitis, unlike allergic bronchopulmonary aspergillosis, is not an eosinophilic lung disease, but mediated by hypersensitivity inflammatory responses that include immunoglobulin (Ig)G.

CASE 1.16 ASBESTOS-RELATED LUNG DISEASE AND PNEUMOCONIOSIS

Instruction

This man has an occupational cause of exertional breathlessness. Please examine his respiratory system and discuss your findings and possible causes.

Recognition

There are fine *inspiratory crackles* affecting both *lower zones*.

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about asbestos exposure. Lower zone fibrosis on chest X-ray, often with benign pleural disease, is typical. Sputum analysis or bronchoalveolar lavage may reveal asbestos bodies but histological diagnosis is not necessary.

What to do next – consider causes

Asbestos causes most occupational dust diseases or pneumoconioses, but consider the causes listed in Figure 1.29: asbestos, coal, silica and beryllium. New industries have generated new forms of interstitial lung disease, e.g. flock-worker's lung in manufacturers of synthetic microfibres (flock) of nylon and metalworker's lung in those exposed to metalworking fluid aerosols.

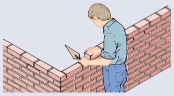
Pneumoconioses								
Asbestos 			Coal dust		Silicon dioxide			Other
Benign pleural disease	Asbestosis	Mesothelioma	Simple coal worker's pneumoconiosis	Complicated coal worker's pneumoconiosis	Simple silicosis Similar to simple coal worker's pneumoconiosis	Accelerated silicosis More rapid and diffuse than simple silicosis	Acute silicosis Like pulmonary oedema Associated with massive exposure	Siderosis (iron oxide) Stannosis (tin) Baritosis (barium) Berylliosis (beryllium) used in nuclear, aerospace and electronics industries

Figure 1.29 Types of pneumoconiosis.

Consider severity / decompensation / complications

Tell the examiners that:

- Finger clubbing is an adverse prognostic sign
- Asbestosis increases the risk of lung cancer and mesothelioma.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

Who is at risk of asbestos-related lung disease?

Asbestos is a mineral silicate that occurs in various forms and is resistant to heat and destruction, which with its fibrous nature meant it could be woven into cloth or incorporated into cement materials, tiles, brake and clutch linings, pipe and boiler insulation, flooring, resins and polymers. Historically high exposures occurred in asbestos mining, milling, and production of asbestos textiles, but the risk was recognised in shipyard workers in the 1950s and the association with mesothelioma appreciated in the 1960s. Today, most with asbestos-related lung disease have a history of exposure such as builders, those working with asbestos insulation (plumbers and electricians), or those cutting asbestos cement sheets. Because of unregulated use of asbestos in developing countries, the incidence of asbestos-related lung disease worldwide is likely to rise.

What are the effects of asbestos on the lung?

The shape of asbestos fibres results in their retention within the lung. Clearance occurs by the mucociliary ladder and phagocytosis, but migration to the pleural surface can occur via the lymphatics. Asbestos-related lung diseases are described in Table 1.18.

Is lung cancer more common with asbestos exposure?

Cumulative asbestos exposure increases the risk of all types of lung cancer independently of cigarette smoking with a synergistic (multiplicative) interaction seen between asbestos exposure and cigarette smoking. Even in the absence of asbestosis, very heavy asbestos exposure may cause lung cancer.

What do you know about the compensation scheme for those eligible with asbestos-related lung disease?

Compensation is through Industrial Injuries Disablement Benefit from the Department of Social Security or a civil law claim for damages from the employer under whose auspices exposure occurred. Under the UK Limitation Act 1980, patients have only 3 years in which to make a civil claim from the date they became aware of a serious injury. Patients should be advised to consult their local Department of Work and Pensions benefit agency for advice on benefits (which may include attendance allowance and disability living allowance). Various charities also provide help and support on compensation. Some compensation requests involve lengthy periods of negotiation (especially civil claims). Former Ministry of Defence personnel are unable to sue the Crown for an industrial injury that occurred before 1987 because of Crown immunity, but may be eligible for a war pension.

What do you know about coal worker's pneumoconiosis (CWP)?

This is related to total coal dust exposure. It is characterised by small or large rounded opacities on chest X-ray with or without focal emphysema, the latter more likely

Table 1.18 Effects of asbestos on the lung

	Benign pleural disease	Asbestosis	Mesothelioma
	Pleural plaques **Diffuse thickening of the pleura** **Benign (exudative) asbestos-related pleural effusion**	**Diffuse interstitial fibrosis**	**Pleural** **Peritoneal (rare)** **Pericardial or tunica vaginalis of testes (very rare)**
Relationship with asbestos exposure	Pleural plaques usually > 20 years after low-intensity exposure Diffuse pleural thickening less specific to asbestos exposure than plaques and may occur after haemothorax, tuberculosis, chest surgery, radiation, infection and drug exposure Benign pleural effusions can occur within 15 years of asbestos exposure but also much later	Usually 20–30 years after substantial exposure Directly related to magnitude and duration of exposure Asbestosis is a typical pneumoconiosis (interstitial lung disease caused by inhaled inorganic dusts)	Usually latent period > 30 years, almost always > 20 years (incidence rising) Disease invariably caused by occupational or domestic asbestos exposure but may occur with minimal exposure although risk is dose related Almost always due to asbestos; common forms of asbestos are serpentine curved fibres – chrysotile (white), amphibole straight fibres – crocidolite (blue), amosite (brown), and anthophyllite Genetic susceptibility to fibre carcinogenesis
Pathology	Fibrosis Pleural plaques comprise layers of hyalinised collagen usually on parietal pleura, and occur in 20–60% of people exposed to asbestos Diffuse pleural thickening usually of visceral pleura	Fibrosis – incomplete phagocytosis of fibres by macrophages with cytokine fibrogenesis	Malignancy of mesothelial cell origin Asbestos bodies in lung but seldom pleura
Clinical features	Pleural plaques asymptomatic (though have been associated with anginal pain) Diffuse pleural thickening may cause breathlessness if extensive Benign pleural effusions are often preceded by episodes of 'asbestos pleurisy'	Insidious onset of breathlessness and reduced exercise tolerance Dry cough Fine late inspiratory crackles in lower zones Finger clubbing 40% (adverse prognostic sign)	Mesothelioma should be considered with any pleural effusion or thickening, especially with a history of asbestos exposure Weight loss is common Chest pain is common, dull, diffuse, progressive, and occasionally pleuritic Breathlessness may be caused by a pleural effusion or circumferential pleural thickening Patients may also present with a palpable chest wall mass, finger clubbing (usually underlying asbestosis) or features of a pericardial effusion Ascites caused by peritoneal mesothelioma and secondary hydropneumothorax are uncommon but recognised presentations
Chest X-ray	Pleural plaques appear as discrete raised calcified areas on parietal pleura (and sometimes pericardium and mediastinum), commonly adjacent to the sixth to ninth ribs and along the surface of the diaphragm but tending not to be evident at the apices or costophrenic angles Diffuse pleural thickening characterised by bilateral smooth continuous pleural density affecting at least 25% of the lateral chest wall (mediastinal border unaffected), usually starting at costophrenic angles with or without blunting (in mesothelioma the pleura is likely to be unilaterally irregularly thickened and the mediastinal border affected) Benign pleural effusions cannot be distinguished from malignant effusions and pleural biopsy is usually needed; benign effusions may resolve spontaneously, often leaving an area of pleural thickening	May be normal but usually bilateral lower zone interstitial changes (with subpleural dominance), often with pleural plaques and thickening	Pleural effusion, lobulated or nodular pleural changes, pleural mass, rib destruction, chest wall involvement, or a small hemithorax as a result of lung entrapment; other features of asbestos exposure may be present
Pulmonary function tests	Normal with pleural plaques Restrictive defect with extensive diffuse pleural thickening	Restrictive defect with reduced gas transfer and exercise-related hypoxaemia	Normal

Table 1.18 Effects of asbestos on the lung—cont'd

	Benign pleural disease			Asbestosis	Mesothelioma		
	Pleural plaques	**Diffuse thickening of the pleura**	**Benign (exudative) asbestos-related pleural effusion**	**Diffuse interstitial fibrosis**	**Pleural**	**Peritoneal (rare)**	**Pericardial or tunica vaginalis of testes (very rare)**
Other tests	HRCT sometimes needed to exclude other cause of a mass, e.g. distinguishes pleural plaques from solid tumours Pleural biopsy seldom needed			HRCT characterised by coarse parenchymal bands, subpleural linear densities, interstitial fibrotic change, and honeycombing in advanced disease (in contrast to idiopathic pulmonary fibrosis, confluent ground-glass changes are rare in asbestosis, and thick band-like opacities more common); the most discriminatory feature is concomitant pleural disease in asbestosis Asbestos bodies in sputum and at bronchoalveolar lavage	Diagnosis confirmed by HRCT and pleural biopsy		
Treatment	Not needed Benign effusions may require drainage if symptomatic			No effective treatment but corticosteroids and immunosuppression considered if rapidly progressive	No effective treatment Discussion at lung multidisciplinary team meeting (chest physicians, surgeons, radiologists, pathologists, oncologists, specialist nurses) Radiotherapy, chemotherapy and biological therapies may modestly reduce tumour bulk Premetrexed and cisplatin may improve survival		
Prognosis	Good Pleural plaques do not undergo malignant change			Progressive Lung cancer risk increased synergistically with smoking 40% die of lung cancer, 10% of mesothelioma	Poor Median survival 8–14 months from diagnosis		
Eligibility for industrial injury benefit	Usually ineligible			Eligible	Eligible		

HRCT, high-resolution computed tomography.

in smokers. There are two types of CWP. Simple CWP refers to asymptomatic small opacities, usually in the upper lobes. Complicated CWP usually occurs on a background of simple CWP and is associated with progressive, upper lobe mass formation (progressive massive fibrosis) causing cough, dyspnoea and sometimes progressive respiratory failure. Lesions may cavitate, mimicking tuberculosis or Wegener's granulomatosis. In Caplan's syndrome, multiple rounded pulmonary nodules develop in patients with rheumatoid arthritis and CWP. There is no effective treatment.

What do you know about silicosis?

This is caused by silicon dioxide, which is highly fibrogenic. High-risk occupations include foundry work, rock tunnelling, coal mining and refractory brick manufacturing. Silicosis is further discussed in Case 2.1.

CASE 1.17 PULMONARY SARCOIDOSIS

Instruction

This 62-year-old man has been increasingly short of breath on exertion. Please examine his chest, neck and axillae and report your findings.

Recognition

There are *bilateral fine inspiratory* (*'Velcro'*) *crackles throughout the lung fields* that do not clear with coughing, together with marked *lymphadenopathy*. There may also be obvious skin (*lupus pernio*; Fig. 1.30) or eye (*uveitis*) disease.

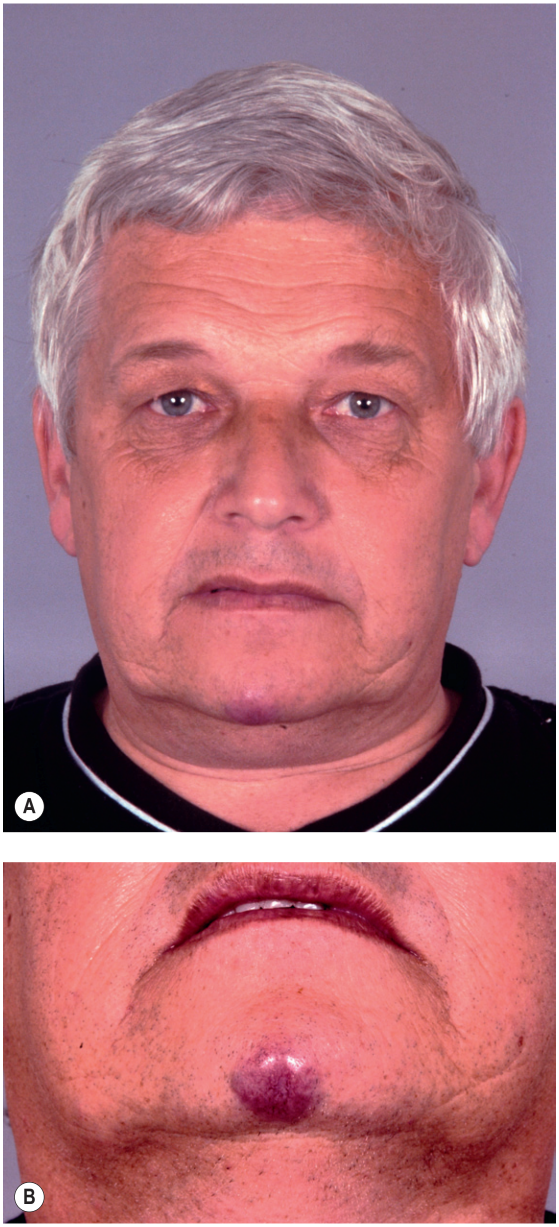


Figure 1.30 Lupus pernio.

Interpretation

Confirm the diagnosis

The most common presentation in white patients is asymptomatic bilateral hilar lymphadenopathy (BHL) on routine chest X-ray or as part of Löfgren's triad (BHL + erythema nodosum + arthritis); fever is common. The second most common presentation is breathlessness or cough but signs may be minimal relative to the pulmonary infiltrates seen on chest X-ray, but any organ system may provide the first presentation, as may hypercalcaemia.

Table 1.19 Extrapulmonary features of sarcoidosis

System	Features
Skin	Erythema nodosum Lupus pernio Itch
Lymphoreticular	Lymphadenopathy (usually painless but can be bulky) Hepatosplenomegaly Deranged liver enzymes Portal hypertension Superior vena cava obstruction
Eyes	Anterior granulomatous uveitis Retinitis / choroidal granulomata (sometimes secondary glaucoma) Sicca
Glands	Parotid, salivary or lacrimal involvement
Neurological	Facial nerve palsy (may be bilateral) Mononeuritis multiplex Lymphocytic meningitis Seizures
Cardiac	Cardiomyopathy Heart block
Renal / metabolic	Interstitial nephritis Nephrolithiasis Hypercalcaemia Hypopituitarism Hypothyroidism Pyrexia (tumour necrosis factor)
Musculoskeletal	Nasal septum perforation Myositis Polyarthritis Cystic dactylitis Bone sclerosis

What to do next – assess other systems

Check for hepatosplenomegaly and skin or eye lesions. Less common extrapulmonary features are also listed in Table 1.19.

Consider severity / decompensation / complications

Situations mandating corticosteroid treatment include:

- Symptomatic pulmonary sarcoidosis
- Critical organ involvement
- Granulomatous vasculitis
- Systemic metabolic effects, e.g. hypercalcaemia, fever
- Local pressure effects.

Consider function

Tell the examiners you would establish the limitations caused by breathlessness.

Discussion

What causes sarcoidosis?

Sarcoidosis is a multisystem granulomatous disease of unknown cause, but there are susceptibility genes on chromosomes 5 and 6 that probably interact with environmental triggers. It affects young adults and has a high prevalence in black Americans and Afro-Caribbeans. There is a seasonal spring peak in Europe with BHL and erythema nodosum. Postulated infectious causes include atypical mycobacteria and pneumonias, herpesvirus 8 and *Propiobacterium acnes*, possibly interacting with polygenic disposition.

What is the pathogenesis of sarcoidosis?

The unknown antigen is presented by an antigen-presenting cell to activate T-helper lymphocytes. This can lead to the release of interleukin-12 (IL-12) and thence interferon-γ (IFN- γ) and tumour necrosis factor-α (TNF-α) via the pro-inflammatory T-helper type 1 (Th1) pathway. Chemokines that facilitate leucocyte attraction and adhesion in sarcoidosis include CCR2 and CCR5. Some patients have an exuberant inflammatory response that will progress unchecked to fibrosis, while in others it will switch off with spontaneous resolution, and this may relate to differences in levels of IL-8, IL-12, TNF-α, fibronectin and collagenase. Granulomata are the classic lesions, containing macrophages, lymphocytes, epithelioid cells and histiocytes, fused to form multinucleate giant cells.

How do the skin manifestations of sarcoidosis differ?

Acute sarcoidosis (granulomatous 'jelly') commonly presents with erythema nodosum as part of Löfgren's triad. This is benign, resolving over weeks, and tends to occur in white people. It involves an exuberant Th1-mediated pro-inflammatory response. Chronic sarcoidosis (granulomatous 'shoe leather') commonly presents as pulmonary fibrosis or lupus pernio, and is immunologically more 'anergic'.

What are the important differential diagnoses of sarcoidosis?

These are usually tuberculosis (TB), which can also cause erythema nodosum, or lymphoma. Treating sarcoid as TB is less dangerous than treating TB as sarcoid! Gallium scanning and biopsy can help confirm a diagnosis of sarcoidosis.

How would you manage sarcoidosis?

Investigations and treatments are listed in Table 1.20.

When would you treat sarcoidosis with corticosteroids or immunosuppression?

Treatment should be instituted for persistent symptoms, important complications or asymptomatic decline in lung function. Whilst there is a tendency to overtreat sarcoidosis (it generally resolves spontaneously) there is also a tendency to undertreat and either not monitor lung

Table 1.20 Management of sarcoidosis

	BHL / Löfgren's triad	Pulmonary infiltration
Blood tests	Normal	Raised serum ACE reflecting granulomatous burden (50%) Hypercalcaemia (10%)
Chest X-ray	BHL	BHL BHL + inflitrates Infiltrates Fibrosis
CT scan	Mediastinal lymph nodes	Reticulonodular pattern with perilymphatic bronchovascular distribution
Pulmonary function tests	Normal or near normal	Restrictive pattern
Biopsy	Only needed if lymphoma or TB suspected (absence of triad)	Transbronchial unless skin lesion or lymph node
Treatment	None NSAIDs for erythema nodosum Corticosteroid eye drops for uveitis Occasionally systemic corticosteroids	Corticosteroid trial

ACE, angiotensin-converting enzyme; BHL, bilateral hilar lymphadenopathy; CT, computed tomography; NSAIDs, non-steroidal anti-inflammatory drugs; TB, tuberculosis.

disease or assume that fibrosis is irreversible when it may in fact coexist with active alveolitis.

No long-term systemic therapy is usually needed for the common presentation of Löfgren's syndrome.

Corticosteroids are very effective and drugs of first choice in suppressing tissue inflammation. They are mandatory for patients with pulmonary infiltrates and impaired lung function (those with low–normal lung function tests should be monitored closely), or for those with critical extrathoracic organ dysfunction or hypercalcaemia. Treatment is for at least 2 years if there is organ dysfunction, with regular pulmonary function tests, chest X-ray and serum angiotensin-converting enzyme (ACE) to monitor improvement and for signs of relapse. Where all is resolving, 2 years might be the limit of treatment needed, but steroid-sparing immunosuppressive agents might be considered after the first 6 months. Where progressing, or where adverse effects are sufficient to prompt early introduction of steroid-sparing agents, methotrexate, azathioprine or hydroxychloroquine are considered. Cytokine-modulating agents have proved disappointing in pulmonary sarcoidosis but may have a role in refractory extrapulmonary disease. Lung transplantation is successful in end-stage fibrotic disease, but sarcoid granulomas may emerge in the allograft.

CASE 1.18 PULMONARY HYPERTENSION

Instruction

This young woman is breathless. Please examine her respiratory system and discuss your findings.

Recognition

There may be one or more of a sequence of signs (Fig. 1.31).

Interpretation

Confirm the diagnosis

This requires investigation, but a loud P2 is helpful. Exertional dyspnoea is often the only symptom. Other symptoms include lethargy, syncope and sometimes nausea.

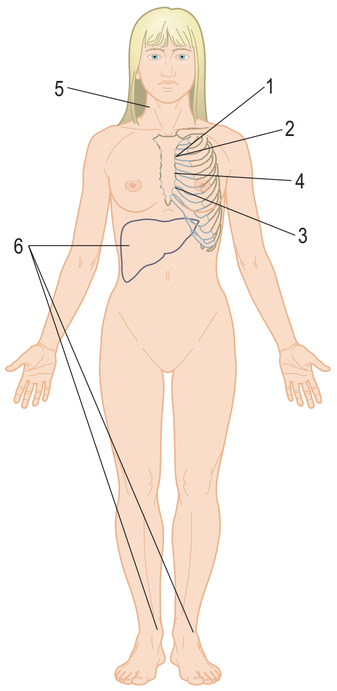
What to do next – consider causes

Tell the examiners possible causes of pulmonary hypertension (Table 1.21).

Consider severity / decompensation / complications

Tell the examiners that severity may be determined by:

- Symptoms and adverse features, e.g. syncopal episodes, extremes of age, rapid progression
- Exercise capacity, e.g. the '6-minute walk' test
- Haemodynamics – pulmonary artery oxygen saturation, cardiac index and right atrial pressure all provide objective haemodynamic information on severity, as does the lack of response to vasodilators at angiography.



1. *Loud* (and later palpable) pulmonary component of S2 (P2)
2. *Pulmonary regurgitation* (*early diastolic murmur* louder in *inspiration* – 'Graham Steel' murmur)
3. Right ventricular overload with a *right ventricular heave* (a *prominent right ventricular impulse* at the left sternal edge) and sometimes a prominent 'a' wave in the JVP – easy to miss
4. *Tricuspid regurgitation* (*pansystolic murmur* at the left sternal edge louder in *inspiration*)
5. '*V*' *wave* in the JVP
6. Effects of right ventricular failure - *tender, pulsatile hepatomegaly* (*sometimes mild jaundice*), *ascites and peripheral and sacral oedema*

Figure 1.31 Signs of pulmonary hypertension. JVP, jugular venous pulse.

Cor pulmonale is right-sided heart failure secondary to pulmonary disease (the final common trigger being pulmonary hypertension).

Consider function

Tell the examiners you would establish exercise capacity.

Discussion

What is pulmonary hypertension?

Pulmonary hypertension (PH)

This is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterisation. The definition of normal haemodynamic response to exercise and the definition of PH on exercise is unclear. PH can be found in multiple clinical conditions.

Pulmonary arterial hypertension (PAH)

This is a clinical condition characterised by the presence of pre-capillary PH in the absence of other causes of

Table 1.21 Clinical classification of pulmonary hypertension

Type	Subtypes
Pulmonary arterial hypertension – formerly known as primary pulmonary hypertension	Idiopathic Heritable: BMPR2, ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia), unknown Drugs and toxins induced (e.g. fenfluramine, dexfenfluramine, toxic rapeseed oil, amphetamines) Associated with pulmonary arterial hypertension – connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia Persistent pulmonary hypertension of the newborn
Pulmonary veno-occlusive disease and / or pulmonary capillary haemangiomatosis	
Pulmonary hypertension due to left heart disease	Systolic dysfunction Diastolic dysfunction Valvular disease
Pulmonary hypertension due to lung diseases and / or hypoxia	Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental abnormalities
Chronic thromboembolic pulmonary hypertension	Now well recognised long after acute PTE, due to fibrotic organised material adherent to endothelium; covert, recurrent small pulmonary emboli are probably under-recognised and may cause stepwise breathlessness
Pulmonary hypertension with unclear and / or multifactorial mechanisms	Haematological disorders: myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1, activin receptor-like kinase type-1; BMPR2, bone morphogenetic protein receptor 2; HIV, human immunodeficiency virus; PTE, pulmonary thromboembolism.

pre-capillary PH such as PH due to heart or lung diseases, chronic thromboembolic PH, or other rare diseases. PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation. PH is often progressive, and pressures generated by the right side of the heart may even exceed systemic arterial pressure. The pressure-overloaded right ventricle initially hypertrophies, and eventually dilates and fails. PAP may paradoxically fall when a failing right ventricle becomes unable to elicit hitherto higher pressures.

What do you know about the pathophysiology of PAH?

All causes of PAH involve remodelling of the small pulmonary arteries. The causes share a similar pathophysiology but have widely different prognoses. Idiopathic PAH (IPAH) is most prevalent in young to middle-aged women. The familial *BMPR2* form is due to a mutation leading to an abnormal transforming growth factor-β receptor. The pathophysiological process starts with environmental factors (e.g. hypoxia, inflammation, toxins, hormones, viruses, shear stresses) and genetic factors (e.g. *BMPR2* mutation, endoglin, ALK-1) conspiring to trigger vascular injury. Vascular injury comprises:

- At the endothelial level, decreased nitric oxide (and other vasodilator molecules such as PG12) and increased endothelin-1 (and other vasoconstrictor molecules such as thomboxanes)
- Inflammation, with production of pro-inflammatory cytokines, e.g. IL-1, IL-6, RANTES
- Smooth muscle cell dysfunction, with smooth muscle cell proliferation, and an increase in many types of molecule, including elastase.

Which investigations may help to confirm PH?

- Diagnosis or screening starts with a low index of suspicion. Early signs are easy to miss. The commonest misdiagnosis is asthma, and patients may be prescribed increasing doses of inhaled asthma therapy in the absence of spirometry suggesting lung disease.
- Eighty per cent of patients with IPAH have an abnormal electrocardiogram (right axis deviation, 'p pulmonale', dominant R in right precordial leads,

right bundle branch block) or chest X-ray (enlarged proximal pulmonary arteries, cardiomegaly), and, if suspected, echocardiography is essential.

- Echocardiography may be normal in IPAH (and is operator dependent), but this is unusual.
- Right heart catheterisation is mandatory for the confirmation of the diagnosis of PAH and is a more accurate determinant of pulmonary artery pressure than echocardiography. One approach is to use echocardiography and diffusing capacity for carbon monoxide (DCLO) as a screening tool: PAP < 30 and DCLO > 50% implying low probability and prompting tests for alternative diagnoses, PAP 30–40 implying intermediate probability prompting further investigation for PAH if DCLO is low, and PAP > 40 warranting further investigation for PAH.
- The prognostic assessment and the definition of clinical status of PAH patients are multidimensional and require the combination of different procedures assessing symptoms (e.g. WHO functional class), exercise capacity (e.g. 6-minute walk test) and right ventricular function (e.g. right heart catheterisation).

How is PH treated?

- An evidence-based treatment algorithm is appropriate only in PAH and not other clinical groups. An acute vasoreactivity test preferably with inhaled nitric oxide is recommended in IPAH. Despite recent progress, the current treatment strategy for PAH remains inadequate. Sequential combination therapy is appropriate. Around 20% respond to vasodilators, and calcium channel blockers (CCBs) are then appropriate therapy. For the 80% who do not respond to CCBs or for those with an initial response who then fail to have a sustained response the following are options: *prostanoids* or prostacyclin analogues, usually delivered as continuous infusion of epoprostenol, subcutaneous (treprostinil) therapy or nebulised (iloprost) therapy – oral beraprost is disappointing; *endothelial antagonists*, which act on endothelin receptors (bosentan, sitaxsentan, ambrisentan); *phosphodiesterase type-5 inhibitors* (e.g. sildenafil, tadafil); *experimental agents*. Atrial septostomy or lung transplantation may also be considered in refractory cases.
- The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease. The specific PAH drugs are not recommended.
- The optimal treatment of the underlying lung disease including long-term oxygen therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases. The specific PAH drugs are not recommended.
- Surgical pulmonary endarterectomy is the recommended treatment for patients with chronic thromboembolic pulmonary hypertension.

CASE 1.19 COR PULMONALE

Instruction

This man is breathless. Please examine his respiratory system and discuss your findings.

Recognition

There is evidence of COPD (see Case 1.1) and cor pulmonale secondary to pulmonary hypertension (see Case 1.18, Fig. 1.32).

Interpretation

Confirm the diagnosis

Cor pulmonale is invariably a clinical diagnosis, and exceedingly common in COPD.

What to do next – consider causes

Tell the examiners of other possible causes of pulmonary hypertension, described in Case 1.18.

Consider severity / decompensation / complications

Tell the examiners that central cyanosis and cor pulmonale imply decompensating lung disease.

Consider function

Tell the examiners you would establish exercise capacity.

Discussion

What is cor pulmonale?

This is right-sided heart failure secondary to pulmonary disease (the final common trigger being pulmonary hypertension).

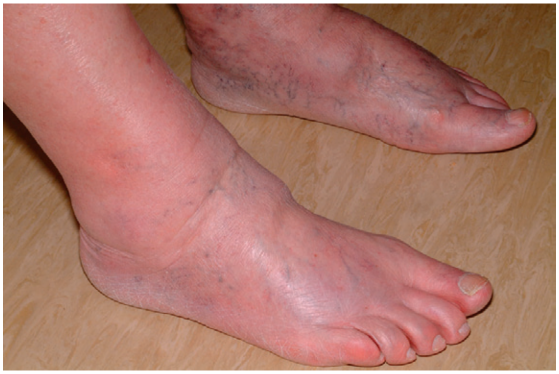


Figure 1.32 Lower limb oedema in cor pulmonale.

How is it treated?

Oxygen and diuretics remain unsatisfactory inroads into what is an advanced condition.

CASE 1.20 PULMONARY EMBOLISM

Instruction

This 72-year-old woman reports pain on inspiration. Please examine her chest and report your findings.

Recognition

There is *tachypnoea* at rest with a respiratory rate of (state) and *tachycardia* with a *loud pulmonary component* to the *second heart sound* (P2). A *pleural rub* is audible at (state location). No other signs are present (Fig. 1.33).

Interpretation

Confirm the diagnosis

Tell the examiners that you would ask about symptoms. Dyspnoea and tachypnoea (respiratory rate ≥ 20 / minute) are the most common.

The frequency of symptoms and signs in a pulmonary embolism (PE) is given in Table 1.22.

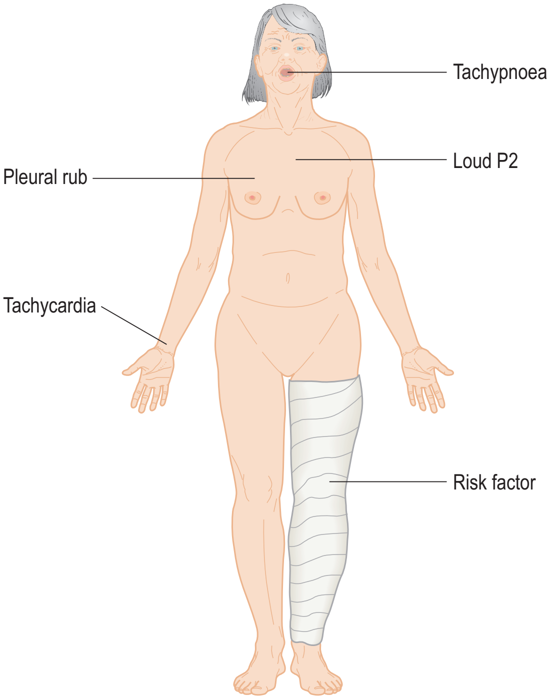


Figure 1.33 Pulmonary embolism.

The haemodynamic effects depend upon the area of the vascular tree involved and on the pre-existing cardiorespiratory state. Acute PE presents in one of four main ways (Table 1.23).

Chronic, covert thromboembolic (often small, subsegmental) disease typically presents with insidious breathlessness over weeks to months due to the increasing burden of recurrent small clots, but can provoke

Table 1.22 Symptoms and signs in pulmonary embolism (PE)

Symptoms	Frequency (%)
Dyspnoea	80
Chest pain (pleuritic)	52
Cough	20
Syncope*	19
Chest pain (substernal)	12
Haemoptysis	11
Signs	
Tachypnoea (>20 / min)	70
Tachycardia (100 / min)	26
Signs of deep vein thrombosis	15
Cyanosis	11
Fever	7

*Syncope used to be considered the presenting feature only in massive PE but has been increasingly recognised as a presentation of smaller PEs. Possible mechanisms include interruption of right ventricular flow, induction of arrhythmias or induction of neurocardiogenic vagal tone, the last often exacerbated by straining, explaining the reason for PE being a first consideration when people collapse 'in the loo'. Dyspnoea is not invariable, and pleuritic pain is only present if the PE is peripheral, irritating the parietal pleura. Hypoxia is likely, and the electrocardiogram may show evidence of right heart strain. Computed tomography pulmonary angiography is recommended in these circumstances.

Table 1.23 Presentation of acute pulmonary embolism (PE)

Presentation	Features
Pulmonary infarction syndrome (60%)	Typically pleuritic pain + / − haemoptysis Pleural rub may be present
Isolated dyspnoea (25%)	Acute breathlessness without haemorrhage or circulatory collapse Typically sudden onset in presence of risk factors
Collapse, poor reserve (10%)	Usually older patients with limited cardiorespiratory reserve in whom a small PE can be catastrophic
Circulatory collapse (5%)	Hypotension + / − syncope Usually due to massive PE with acute right-sided heart failure

Box 1.19 Risk factors for pulmonary embolism

Major (relative risk 5–20)

- Major and abdominal surgery
- Lower limb orthopaedic surgery
- Obstetric causes – late pregnancy, Caesarean section, pre-eclampsia
- Malignancy – pelvic, abdominal, metastatic
- Lower leg fracture or varicose veins
- Previous proven venous thromboembolism (VTE)

Minor (relative risk 2–4)

- Cardiovascular – heart failure, hypertension, congenital heart disease, central venous access
- Oestrogens – oral contraceptive pill, hormone replacement therapy
- Other – occult malignancy, chronic obstructive pulmonary disease, neurological disability, obesity, thrombotic and myeloproliferative disorders, nephrotic syndrome, inflammatory bowel disease

There is a high risk of VTE in hospital inpatients with a wide variety of acute medical conditions comparable with that seen after major surgery – hence prophylactic low-molecular-weight heparin is used routinely in hospitalised patients, especially those who are older, bed-bound or sedentary.

marked deterioration in those with brittle lungs. It is under-recognised.

What to do next – consider causes

Risk factors for venous thromboembolism (VTE) are listed in Box 1.19.

Consider severity / decompensation / complications

Circulatory collapse indicates massive PE.

Consider function

Tell the examiners you would establish exercise capacity.

Discussion

Why is pulmonary embolism (PE) important?

The annual incidence is 60–70 per 100 000. Untreated mortality is about 30% and it is the commonest cause of death after elective surgery and the commonest cause of maternal death in the UK.

What causes PE?

PE refers to obstruction of part of the vascular tree, usually because of a thrombus from a distant site, usually a deep vein thrombosis (DVT) in the leg and pelvis. Up to 50% of patients with a clinically obvious DVT have a high-probability V/Q scan and around 70% of patients with proven PE have a proximal DVT. Rare causes include air, amniotic fluid and fat embolisms.

Box 1.20 When to test for thrombophilia

- Patients under 50 with recurrent idiopathic pulmonary embolism (50% have an identifiable thrombophilia)
- Patients with a strong family history (several family members in more than one generation) of proven pulmonary thromboembolism

Does smoking increase the risk of VTE?

There is, surprisingly, little evidence for this.

What do you know about 'economy class syndrome' as a risk factor?

Long-distance sedentary travel is a risk factor for VTE. A 2001 study of 135.29 million passengers showed an incidence of 4.8 cases per million for travel over 10 000 km, 1.5 per million for travel over 5000 km and up to 10 000 km and 0.01 per million under 5000 km. Air quality may have a bearing since watching television for an equivalent time period seems to carry less risk of PE (although a higher risk of obesity!).

What do you know about inherited thrombophilias?

These are discussed in Case 2.37; 25–30% of patients with PE have an identifiable inherited thrombophilia that must usually interact with an acquired risk factor to provoke VTE.

When might you consider thrombophilia testing?

The two main situations are listed in Box 1.20.

When are investigations for occult malignancy justified?

Occult cancer is present in 7–12% of patients with idiopathic VTE. Screening is recommended in unprovoked PEs (debatable) or when suspected clinically, or on chest X-ray or routine blood tests. These patients are more likely to have a poor prognosis because of regional or distant metastases. Earlier identification of malignancy is possible with screening but it is not known whether this impacts on survival.

Why does hypoxia occur in PE?

This is the result of reduced cardiac output, low mixed venous pO_2 and higher perfusion to the remaining alveoli, leading to mismatching of ventilation and perfusion (V/Q). Hypoxia is greater in those with a larger pre-morbid V/Q spread, e.g. pre-existing lung disease; a hitherto healthy person may thus not be hypoxic. Hypoxia is often disproportionate to the degree of lung affected, however, and this may be because of hitherto ill-understood inflammatory responses to PE, or sometimes due to showers of sub-radiographic emboli causing wider micro-damage. This said, if there is marked hypoxia with haemodynamic stability, the question must arise as to the possibility of a patent foramen ovale causing right to left shunting of blood.

How would you determine the clinical probability of PE?

The prevalence of PE in people in whom the diagnosis is suspected is only about 15%. PE cannot be safely diagnosed or excluded by history and examination; it is necessary to combine clinical (pre-test) probability with investigations to determine a post-test probability. Various prediction criteria (Table 1.24) have been used, including the Wells and Geneva scores. In 2001, Wells published three risk categories. A modified extended version using a cut-off of 2 points was then proposed. More recently, further modification to a cut-off of 4 points creating two categories of risk has been used. The revised Geneva score has been shown to be as effective as the Wells score. The simplified Wells score and simplified Geneva score replaced the weighted scores for each parameter with a 1-point score for each parameter to reduce the likelihood of error in clinical settings and appear to be valid.

The 2003 British Thoracic Society guidelines offered a simplified model for determining clinical probability (Table 1.25). The vast majority of patients with PE have at least one of dyspnoea, chest pain or hypoxia. Experienced clinicians and their instinct are as accurate as the pre-test clinical probability score.

How may suspected acute PE be confirmed?

The diagnosis of acute PE embraces the pre-test clinical probability score and several investigations.

D-dimer testing

D-dimers reflect thrombin and fibrin generation and are released as a result of subsequent plasmin activation with fibrinolysis and indicate intravascular thrombosis. D-dimer testing should not be used as a screening test as the majority of patients in an acute medical setting have a raised D-dimer, especially as hospital stay extends (venepuncture and venous stasis from bed rest). A properly validated D-dimer test determines which tests are ordered and how they are interpreted. Validated D-dimer assays include the SimpliRED agglutination test (used when there is low clinical probability) and the Vidas ELISA test or MDA latex test (used when there is low or intermediate clinical probability). Interpretation of D-dimer testing is outlined in Box 1.21.

Box 1.21 **Interpretation of D-dimer testing (post-test probability)**

- A negative D-dimer combined with a low (intermediate with some assays) clinical probability is usually sufficient to exclude a pulmonary embolism (92% sensitivity for low and intermediate clinical probability).
- A raised D-dimer does not imply the presence of venous thromboembolism because it may be raised in many clinical settings; that is, only a negative result is of value (D-dimers have only negative predictive value).
- D-dimer testing should not be performed if clinical probability is high, when imaging should be the next step.

Computed tomography pulmonary angiography (CTPA)

Multidetector CTPA is the first-line imaging technique for non-massive PE. CTPA can diagnose PE with 98% sensitivity (< 3% of scans are indeterminate), establish possible alternative diagnoses and exclude significant PE. The ability of CTPA to detect isolated subsegmental PE is improving. In patients with a high clinical probability but a negative CTPA it may be reasonable to conclude that PE has been excluded, consider further imaging such as leg ultrasound or invasive angiography, or seek specialist advice. However, many physicians would not be dissuaded by a negative CTPA with high clinical suspicion, and consider bilateral leg ultrasound or venography and anticoagulation. Leg ultrasound is an alternative to lung imaging in patients with clinical evidence of DVT and suspected PE. Identification of DVT may be sufficient to confirm VTE, but compression ultrasound is of limited accuracy in detecting asymptomatic proximal DVT and should not be relied on for excluding subclinical DVT. Massive PE may be diagnosed by CTPA or echocardiography. CTPA involves a lower fetal radiation dose than V/Q scanning.

Isotope ventilation/perfusion (V/Q) scan

Isotope V/Q scanning may be considered as the initial imaging investigation if there is no significant concurrent cardiopulmonary disease and the chest X-ray is normal (or, more importantly, no history of lung disease), but this method has largely been superseded by CTPA. A low-probability scan combined with a low clinical probability excludes PE. A high-probability scan combined with a high clinical probability diagnoses PE (a significant minority of high-probability results are false positives; therefore, a high-probability scan in the absence of high clinical probability warrants further investigation). All other combinations (i.e. non-diagnostic scan or discordant clinical and scan probability) require CTPA, and only 30–50% of intermediate scans reflect PE.

What might the electrocardiogram show in acute PE?

The electrocardiogram may show non-specific changes, sinus tachycardia most commonly, or atrial fibrillation, right axis deviation, right bundle branch block, anterior T-wave inversion (indicating right ventricular strain) or, uncommonly, the $S_1Q_3T_3$ pattern.

Table 1.24 Wells clinical prediction rule for clinical probability of pulmonary embolism (PE)

	Revised Geneva score	**Simplified Geneva score**		**Wells score**	**Simplified Wells score**
Variable	**Points**	**Points**	**Variable**	**Points**	**Points**
Predisposing factors			*Predisposing factors*		
Age 65 years or over	1	1	Previous DVT or PE	1.5	1
Previous DVT or PE	3	1	Recent surgery or immobilisation	1.5	1
Surgery or fracture within 1 month	2	1	Cancer	1	1
Active malignancy	2	1			
Symptoms			*Symptoms*		
Unilateral lower limb pain	3	1	Haemoptysis	1	1
Haemoptysis	2	1			
Signs			*Signs*		
Heart rate 75–94 beats per minute	3	1	Heart rate greater than 100 beats per minute	1.5	1
Heart rate 95 or more beats per minute	5	+ 1 (heart rates 75–94 receive 1 point, heart rates higher than 94 receive a further point, i.e. 2 points in total)	Clinical signs of DVT	3	1
Pain on deep palpation of lower limb and unilateral oedema	4	1			
			Clinical judgement		
			Other diagnosis less likely than PE	3	1
	Clinical probability			*Clinical probability*	
	Low 0–3 Intermediate 4–10 High ≥ 11			Former score interpretation Low < 2 Intermediate 2–6 High > 6 Dichotomised score interpretation PE unlikely ≤ 4 PE likely > 4	PE unlikely ≤ 1 PE likely > 1

DVT, deep vein thrombosis.

Table 1.25 Simplified model for determining clinical probability of pulmonary embolism (PE)

Symptoms or signs compatible with PE		**Is another diagnosis unlikely?**	
		No	**Yes**
Is there a major risk factor?	**No**	Low risk	Intermediate risk
	Yes	Intermediate risk	High risk

What might the chest X-ray show in acute PE?

Non-specific changes are common, and small pleural effusions occur in about 40% of patients.

What might the arterial blood gases show in acute PE?

Hypoxia and hypocapnia are common.

When would you consider echocardiography?

This is diagnostic in massive PE, and is a useful bedside test.

When is low-molecular-weight heparin (LMWH) started in PE?

LMWH has revolutionised the early treatment of non-massive PE, and allows some patients to be discharged with daily outpatient investigation and treatment. It is superior to unfractionated heparin, dosing and administration are simple, and monitoring is not required except in obesity, pregnancy and renal failure. LMWH should be instituted in patients with intermediate or high clinical probability before imaging. The efficacy and safety of LMWH in massive PE has not yet been established, and unfractionated heparin should be considered.

For how long should warfarin be administered following a diagnosis of PE?

First idiopathic PE

Oral anticoagulation with a target international normalised ratio (INR) of 2.0–3.0 is administered for 3–6 months for a first PE, 6 months if idiopathic but possibly less if provoked with the provocation removed. Whilst duration of treatment is uncertain, emerging evidence suggests that 6 months provides no more benefit than 3 months, but increases the risk of serious bleeding. The Prevention of Recurrent Venous Thromboembolism (PREVENT) and Extended Low-Intensity Anticoagulation for Thrombo-Embolism (ELATE) trials have shown that low-intensity warfarin significantly protects against recurrent VTE but there is no consensus as to which patients to treat.

First PE with persisting risk factors or life-threatening first PE

A first PE with persisting risk factors warrants lifelong anticoagulation. Most physicians would also recommend lifelong anticoagulation after a life-threatening first PE.

Recurrent idiopathic PE

Lifelong anticoagulation is recommended for recurrent idiopathic PE.

Should there be an overlap between warfarin introduction and heparin withdrawal?

Yes. Heparin should be continued for a few days after warfarin has been introduced (at least where anticoagulation is treating active clots as in VTE or mural thrombus, though not when warfarin is being started to prevent clots as in atrial fibrillation). Warfarin inhibits hepatic synthesis of prothrombotic factors II, VII, IX and X, but also inhibits the production of the natural anticoagulant promoter protein C and its cofactor protein S. The half-life of proteins C and S is short, and thus in the first few days of warfarin therapy a state of procoagulation may be induced, especially in patients with underlying protein C or S deficiency.

Is warfarin used in patients with cancer?

The CLOT study showed that LMWH was superior to warfarin over 6 months in preventing recurrent VTE in patients with acute PE in the setting of cancer.

What is recommended for prophylaxis of PE for long-haul flights?

Mobility should be encouraged. Aspirin or LMWH is supported by limited evidence.

Is there a role for other anticoagulants in treating PEs?

Ximelagatran, a direct thrombin inhibitor, was withdrawn because of liver toxicity. The role of factor X inhibitors and other thrombin inhibitors is evolving.

What is the place of inferior vena cava filters in PE?

This is limited to a very small number of cases of recurrent PE despite adequate anticoagulation. Clotting of the filter is common.

What is the place of thrombolytic therapy in PE?

Thrombolysis is the first-line treatment for PE with shock (massive PE). A 50 mg bolus of alteplase may be instituted on clinical grounds if cardiac arrest seems imminent, and CTPA or bedside echocardiography is the urgent investigation of choice. A patient stable enough for a CTPA is often not clinically compromised enough to warrant consideration of thrombolysis. Since thrombolysis carries a fatal haemorrhage rate of around 2.1%, it should not be used in patients with non-massive PE, although in absolute numbers most deaths from PE occur in patients presenting with non-massive PE which subsequently progresses to massive PE and there is research emphasis on identifying this subgroup (e.g. troponin levels, brain natriuretic peptide (BNP), *N*-terminal BNP, D-dimer, hypoxaemia). Invasive approaches such as thrombus fragmentation may be considered. The evidence base for thrombolysis in PE is limited, the most compelling indication being persistent hypotension.

How does management of suspected and confirmed PE differ in pregnancy?

Standard pre-test clinical probability should be determined in the same way, recognising that pregnancy is a major risk factor. D-dimer testing is of no value because it rises after about 6 weeks' gestation and is elevated until about 3 months post-partum. A chest X-ray is mandatory, and should not be delayed by concerns about fetal radiation. V/Q scanning and CTPA carry greater risks but the risk to mother and unborn child of delayed diagnosis is greater. A lone Q scan may be safest. Warfarin is contraindicated in pregnancy. LMWH is used from diagnosis until 6–12 weeks post-partum.

May patients with PE be managed as outpatients?

The Pulmonary Embolism Severity Index (PESI) stratifies risk as low or high, and has some variations. A simplified PESI variation scores 1 point for each of age > 80 years, history of cancer, chronic cardiopulmonary disease, heart rate > 110/minute, systolic blood pressure < 100 mmHg and arterial oxygen saturation < 90%; a score of 0 is low risk, whilst 1 or more is high risk, those with low risk being appropriate for consideration of outpatient treatment.

CASE 1.21 PLEURAL EFFUSION

Instruction

This 70-year-old woman is breathless. Please examine her chest and report your findings.

Recognition

The *trachea* is *deviated to the opposite side* (if large pleural effusion). There is *stony dullness* to percussion. *Breath sounds* and *vocal resonance* are *reduced* (Fig. 1.34).

Interpretation

Confirm the diagnosis

Consider the other causes of dullness at the lung base (Case 1.3).

What to do next – consider causes

Tell the examiners that it may be an exudate or transudate (Table 1.26). Many drugs have been reported as causing a pleural effusion, usually an exudate, and include amiodarone, nitrofurantoin, phenytoin and methotrexate.

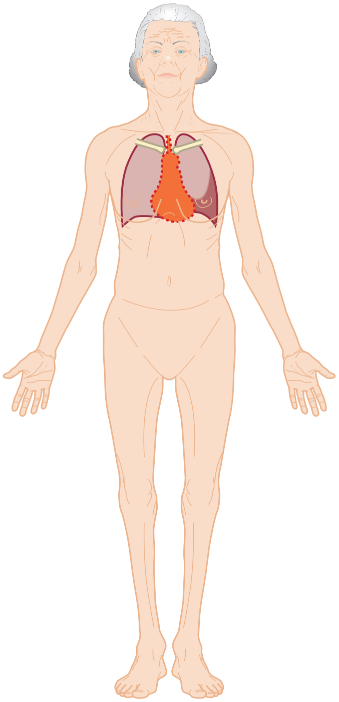


Figure 1.34 Pleural effusion.

Consider severity/decompensation/complications

This depends largely on the underlying cause.

Consider function

Tell the examiners you would establish exercise tolerance.

Discussion

What is the approach to investigation and management of a unilateral pleural effusion?

This is outlined in Figure 1.35.

Pleural aspiration

Aspiration should not be performed for bilateral effusions in a clinical setting strongly suggestive of a transudate unless there are atypical features or they fail to respond to therapy. All unilateral pleural effusions require further investigation, starting with aspiration. Large effusions (> 50% of hemithorax volume) may be aspirated easily without ultrasound guidance, but generally ultrasound guidance is recommended and can also confirm any septations. Aspiration rather than intercostal drainage is preferable and complete drainage (except where infection is known to be the cause) is not recommended as it makes

Table 1.26 Causes of transudates and exudates

Transudates (< 30 g / l protein) **Tend to be bilateral; cause usually non-pulmonary**	**Exudates (> 30 g / l protein)** **Tend to be unilateral**
Left ventricular failure (*raised jugular venous pulse, pulmonary oedema, third heart sound*); chronic effusions may become exudates; about 50% may be unilateral	Bronchial carcinoma / mesothelioma (*cachexia, clubbing, tar staining*)
Nephrotic syndrome (*generalised / facial / periorbital oedema*)	Infection – parapneumonic effusion, empyema, tuberculosis
Hepatic failure (*signs of chronic liver disease*); in addition to hypoproteinaemia, right-sided diaphragmatic lymphatic channels may open secondary to ascites and contribute to the effusion	Pulmonary embolism (*pleural rub, deep vein thrombosis*) – 10–20% are transudates
Hypothyroidism (*myxoedematous*)	Inflammation (autoimmune connective tissue disease, vaculitis)
Peritoneal dialysis	Benign asbestos effusion
Meigs' syndrome, with benign ovarian fibroma	Subphrenic abscess
Constrictive pericarditis	Oesophageal perforation
Superior vena cava obstruction	Pancreatitis
	Post-cardiac surgery
	Chylothorax or pseudochylothorax
	Drug-induced
	Yellow nail syndrome (yellow nails and lymphatic hypoplasia)

Box 1.22 **Light's criteria (≥ one of these favours an exudate)**

- Pleural fluid total protein : serum total protein > 0.5
- Pleural fluid lactate dehydrogenase (LDH) : serum LDH > 0.6
- Pleural fluid LDH more than two-thirds the upper limit of normal serum LDH

further investigation more difficult. In symptomatic pleural effusions, such as those causing breathlessness, large-volume (e.g. 1 litre) thoracocentesis is usually sufficient for diagnostic and therapeutic purposes.

Pleural fluid analysis

- Pleural fluid should be sent for protein, lactate dehydrogenase, Gram stain, cytology and microbiological culture.
- The appearance and odour should be recorded.
- A pleural fluid haematocrit is helpful in the diagnosis of haemothorax.
- Light's criteria should be used to distinguish between an exudate and transudate (Box 1.22), using the total protein and lactate dehydrogenase measured in both blood and pleural fluid (protein concentration may be reliable if pleural protein is < 25 g/l or > 35 g/l).
- Pleural fluid cell proportions are helpful in narrowing the differential diagnosis but none is disease specific. Any long-standing pleural effusion tends to become populated by lymphocytes. Pleural malignancy, cardiac failure and tuberculosis are common specific causes of lymphocyte-predominant effusions.
- In non-purulent effusions, when pleural infection is suspected, pleural fluid pH should be measured. In a parapneumonic effusion, a pH < 7.2 indicates the need for tube drainage.
- Routine measurement of pleural fluid amylase, or its isoenzymes, is not warranted. It can, however, be useful in suspected cases of oesophageal rupture or effusions associated with pancreatic diseases.
- Malignant effusions can be diagnosed by pleural fluid cytology in about 60% of cases. The yield from sending more than two specimens (taken on different occasions) is very low and should be avoided.
- Immunocytochemistry should be used to differentiate between malignant cell types and can be very important in guiding oncological therapy.

Imaging

Computed tomography (CT) scans should be performed in:

- All undiagnosed exudative pleural effusions, and can be useful in distinguishing malignant from benign pleural thickening
- Complicated pleural infection when initial tube drainage has been unsuccessful and surgery is considered.

CT scans should be performed with contrast enhancement of the pleura and before complete drainage of pleural fluid.

Invasive investigations

Percutaneous pleural biopsy

When investigating an undiagnosed effusion where malignancy is suspected and areas of pleural nodularity are shown on contrast-enhanced CT, an image-guided needle biopsy is the percutaneous pleural biopsy method of choice. Abrams needle biopsies are diagnostically useful only in areas with a high incidence of TB.

Thoracoscopy

Thoracoscopy with biopsy is the investigation of choice in exudative pleural effusions where a diagnostic pleural aspiration is inconclusive and malignancy is suspected.

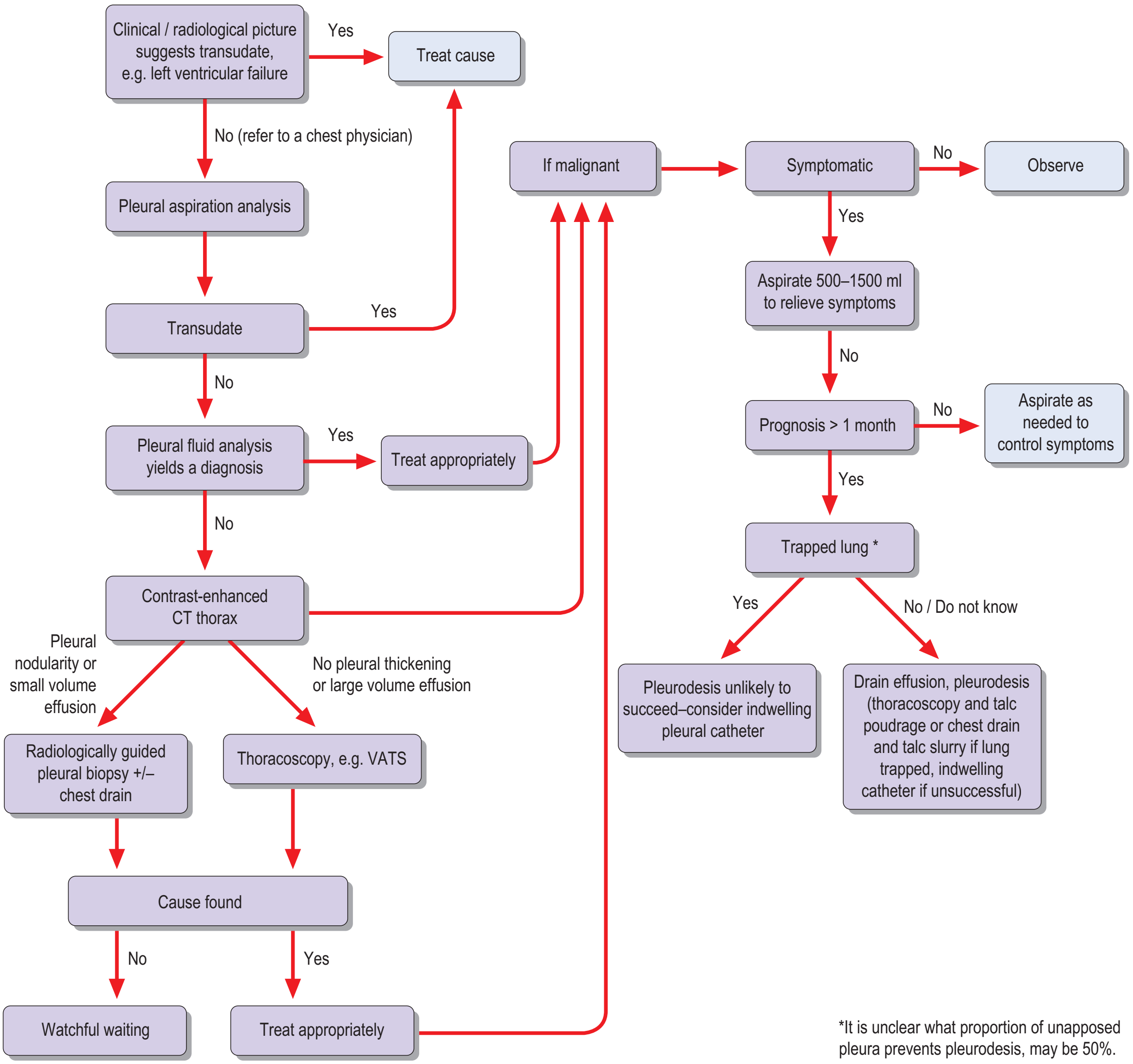

Clinical / radiological picture suggests transudate, e.g. left ventricular failure
Yes
Treat cause
No (refer to a chest physician)
Pleural aspiration analysis
Transudate
Yes
No
Pleural fluid analysis yields a diagnosis
Yes
Treat appropriately
No
Contrast-enhanced CT thorax
Pleural nodularity or small volume effusion
No pleural thickening or large volume effusion
Radiologically guided pleural biopsy +/– chest drain
Thoracoscopy, e.g. VATS
Cause found
No
Yes
Watchful waiting
Treat appropriately
If malignant
Symptomatic
No
Observe
Yes
Aspirate 500–1500 ml to relieve symptoms
No
Prognosis > 1 month
No
Aspirate as needed to control symptoms
Yes
Trapped lung *
Yes
No / Do not know
Pleurodesis unlikely to succeed–consider indwelling pleural catheter
Drain effusion, pleurodesis (thoracoscopy and talc poudrage or chest drain and talc slurry if lung trapped, indwelling catheter if unsuccessful)
*It is unclear what proportion of unapposed pleura prevents pleurodesis, may be 50%.

Figure 1.35 Investigation and management algorithm for unilateral pleural effusion. VATS, video-assisted thoracoscopic surgery.

Bronchoscopy

Bronchoscopy should be considered if there is haemoptysis, or clinical or radiographic features suggest bronchial obstruction.

Specific conditions and tests

Tuberculous pleurisy

When pleural biopsies are taken, they should be sent for both histological examination and culture to improve the diagnostic sensitivity for tuberculosis.

Rheumatoid arthritis-associated pleural effusions

Most chronic pleural effusions secondary to rheumatoid arthritis have a very low glucose level of less than 1.6 mmol/l (29 mg/dl).

Chylothorax and pseudochylothorax

If a chylothorax or pseudochylothorax is suspected, pleural fluid should be tested for cholesterol crystals and chylomicrons and the pleural fluid triglyceride and cholesterol levels measured.

What is the approach to management of a malignant pleural effusion?

This is outlined in Figure 1.35.

Investigation

The majority of malignant effusions are symptomatic. Large pleural effusions are most commonly due to malignancy – lung cancer, metastatic cancer or mesothelioma; diagnostic aspiration has only a 60% sensitivity for malignancy and if cytology is negative then CT scanning should be performed before drainage because it has a high sensitivity for malignancy. Pleural fluid should initially only be aspirated for symptom relief, leaving some fluid for safe CT-guided biopsy or thoracoscopy, these tests having higher diagnostic yields for malignant pleural disease.

- CT-guided biopsy is used when pleural thickening is present, with only a small volume of pleural fluid; open thoracotomy and biopsy may be needed where CT-guided biopsy is inconclusive.
- Thoracoscopy (e.g. video-assisted thoracoscopy) should be used with more substantial fluid volumes, if no nodularity is revealed on CT, and where both diagnostic and therapeutic (talc pleurodesis) effects are needed.

Management

- Advice should be sought from the respiratory/respiratory multidisciplinary team.
- Observation is recommended if a patient is asymptomatic and the tumour type is known.
- Pleural effusions treated by aspiration alone are associated with a high rate of recurrence of effusion at 1 month, so aspiration is not recommended if life expectancy is greater than a month. Caution should be taken if removing more than 1.5 litres on a single occasion.
- Other than in patients with a very short life expectancy, small-bore chest tubes (10–14 F) followed by pleurodesis are preferable to recurrent aspiration. Intercostal drainage should be followed by pleurodesis to prevent recurrence unless lung is significantly 'trapped' (pleural apposition cannot be achieved).
- Large pleural effusions should be drained in a controlled fashion to reduce the risk of re-expansion pulmonary oedema. In patients where only partial pleural apposition can be achieved, chemical pleurodesis may still be attempted and may provide symptomatic relief. In symptomatic trapped lung, indwelling pleural catheters offer a more attractive therapeutic approach than recurrent aspiration. Once drainage and lung re-expansion have been radiographically confirmed, pleurodesis should not be delayed.
- Talc is the most effective sclerosant for pleurodesis. Graded talc should always be used in preference to ungraded talc as it reduces the risk of arterial hypoxaemia. Bleomycin is an alternative sclerosant with modest efficacy. Pleuritic chest pain and fever are the most common side effects.
- Patients with proven or suspected mesothelioma should receive prophylactic radiotherapy to the site of thoracoscopy, surgery or large-bore chest drain insertion.
- Intrapleural instillation of fibrinolytic drugs is recommended for the relief of distressing dyspnoea due to multiloculated malignant effusion resistant to simple drainage.
- In patients with good performance status, thoracoscopy is recommended for diagnosis of suspected malignant pleural effusion and for drainage and pleurodesis of a known malignant pleural effusion. Thoracoscopic talc poudrage should be considered for the control of recurrent malignant pleural effusion.
- Ambulatory indwelling (e.g. *Pleurex*) pleural catheters are effective in controlling recurrent and symptomatic malignant effusions in selected patents.

How should a haemothorax be managed?

These may be secondary to trauma or disease, usually malignancy, and cardiothoracic surgeons should be consulted. Any significant haemothorax may require thoracoscopy (e.g. video-assisted thoracoscopic surgery) to ensure adequate evacuation and reduce the risk of subsequent empyema. Haemodynamic instability suggests ongoing bleeding.

What is the approach to investigation and management of pleural infection?

Up to 57% of patients with pneumonia develop a parapneumonic pleural effusion, varying in size from very small and not visible on chest X-ray to large causing ventilatory compromise. Most are reactive, non-infected, 'simple effusions', but approximately 40% are 'complicated effusions', and empyema when pus cells are evident macroscopically. Pleural infection usually occurs with pneumonia, but surgery, trauma and extension of suppuration from elsewhere (e.g. subphrenic abscess, oesophageal rupture) are possible causes. A chest physician or thoracic surgeon should be involved in the care of all patients requiring chest tube drainage for pleural infection. Adequate nutrition and thromboprophylaxis are important.

Clinical features

Patients may present with sepsis and features of pneumonia, or more indolent constitutional features such as weight loss and night sweats, with parietal pleural inflammation causing pleuritic chest pain. Unresolving pneumonia, or ongoing sepsis and a non-improving white cell count or C-reactive protein in patients with pneumonia, after 3 or more days, may indicate progression to pleural infection. All patients with suspected pleural infection should have blood cultures for aerobic and anaerobic bacteria performed.

Pleural ultrasound

Echogenic (internal echoes within fluid) appearances suggest an exudative effusion, and heavily echogenic fluid suggests blood or pus. Septated (visible lines within pleural fluid) appearances suggest an exudative effusion and septations particularly suggest low pH, low glucose and high lactate dehydrogenase. Septation density may predict drainage success, but even heavily septated effusions may drain well.

Computed tomography (CT)

Pleural thickening, enhancement and increased attenuation of subcostal fat suggest pleural infection, and CT may particularly help distinguish pleural infection from a peripheral pulmonary abscess.

Pleural fluid aspiration

All patients with a pleural effusion in association with sepsis or a pneumonic illness require diagnostic pleural fluid sampling, which can differentiate the effusion into a simple non-infected effusion, a complicated infected effusion or empyema (Table 1.27). Pleural fluid pH is an important predictor of pleural infection, although malignancy and other causes of pleural inflammation may also cause pH values < 7.2. Glucose and lactate dehydrogenase values do not improve diagnostic reliability and should be performed only if pH values are unavailable. Culture of fluid is important; 60% of causative organisms are aerobic (e.g. *Streptococcus* – though *Streptococcus pneumonia* is not that common, *Staphylococcus*, Gram-negatives) and meticillin-resistant *Staphylococcus aureus*, Enterobacteriaceae, enterococci and *Pseudomonas* should be considered in hospitalised patients. Anaerobes and mixed growths are common.

Indications for pleural fluid drainage in pleural infection

The following should receive prompt pleural space chest tube drainage in patients with suspected pleural infection:

- Frankly purulent or turbid / cloudy pleural fluid on sampling
- The presence of organisms identified by Gram stain and / or culture from a non-purulent pleural fluid sample (indicates that pleural infection is established)
- Pleural fluid pH < 7.2 in patients with suspected pleural infection.

Parapneumonic effusions that do not fulfil any of these criteria for chest tube drainage could be treated with antibiotics alone provided clinical progress is good. Poor clinical progress during treatment with antibiotics alone should lead to repeat pleural fluid sampling and probably chest tube drainage. Patients with a loculated

Table 1.27 Parapneumonic effusions and empyema

Problem	'Simple' parapneumonic effusion	'Complicated' parapneumonic effusion	Empyema
Frequency	Up to 57% of people with pneumonia	Smaller proportion progress to this	Smaller proportion progress to this
What it is	Following dry pleuritis, pulmonary interstitial fluid crosses visceral pleura, accompanied by pro-inflammatory cytokine cascade	Infection of pleural space	Pus in pleural space Thick pus if more advanced, often with fibrin strands + / – loculation After about 8 weeks pleura thickens and pleural 'cortex' ('peel' or 'rind'), an inelastic membrane adherent to lung, develops
Diagnosis (pleural fluid analysis)	pH normal (≥ 7.2) LDH ≤ 1000 U / l (normal) Glucose ≥ 2.2 mmol / l (normal)	pH < 7.2 LDH > 1000 IU / l Glucose < 2.2 mmol / l Neutrophils Culture (25% positive)	Pus (pH, glucose or LDH not usually measured) Culture (70% positive)
Treatment	Simple aspiration (need not be to dryness)	Aspiration to dryness with antibiotics (medical team) Historically large-bore (24–32 F) chest tube, but small-bore (8–14 F) as good if flushed 6-hourly with 30 ml saline and produces less pain	Possible 'medical' drainage with surgical input Place of surgery not well defined but indicated if medical management fails with persistent fever. Effective drainage of pleural space required, with video-assisted thoracoscopic surgery or thoracotomy if loculations; fibrinolytics not recommended

LDH, lactate dehydrogenase.

pleural collection should receive early chest tube drainage. Large non-purulent effusions could be drained by aspiration and/or chest tube if required for symptomatic benefit.

Antibiotics

All patients should receive antibiotics targeted to treat the bacterial profile of modern pleural infection, and based on local antibiotic policies and resistance patterns. Antibiotics to cover anaerobic infection should be used in all patients, except those with culture-proven pneumococcal infection. Macrolide antibiotics are not indicated unless there is objective evidence for, or a high clinical index of suspicion of, 'atypical' pathogens. Penicillins, penicillins combined with β-lactamase inhibitors, metronidazole and cephalosporins penetrate the pleural space well. Aminoglycosides should be avoided. Empirical antibiotic treatment for hospital-acquired empyema should include treatment for MRSA and anaerobic bacteria. Intravenous antibiotics should be changed to oral therapy once there is evidence of improvement in sepsis. Intrapleural antibiotics are not recommended. Prolonged courses of antibiotics may be necessary.

Persistent sepsis and pleural collection

Patients with persistent sepsis and a residual pleural collection should undergo further radiological imaging and be discussed with a thoracic surgeon to consider all possible surgical options.

CASE 1.22 PLEURAL RUB

Instruction

This 46-year-old woman reports pain on inspiration. Please examine her chest and report your findings.

Recognition

There is a superficial *scratching/grating/creaking sound on deep inspiration* (like the crackle of leaves underfoot on an autumn forest floor, or the crunching underfoot of freshly fallen snow!). This is a pleural rub.

Interpretation

Confirm the diagnosis

A pleural rub sounds 'close to the stethoscope' and does not change with coughing.

What to do next – consider causes

The two common causes are pulmonary embolism (tachypnoea, tachycardia, loud P2) and pneumonia (signs of consolidation).

Consider severity/decompensation/complications

Tell the examiners that you would urgently assess haemodynamic stability in suspected PE and the CURB score in suspected pneumonia.

Consider function

Tell the examiners you would establish exercise capacity.

Discussion

How might you distinguish a pleural friction rub from a pericardial friction rub?

The latter continues if the patient holds their breath.

CASE 1.23 PNEUMOTHORAX

Instruction

This young man was brought to hospital with sudden breathlessness. Please examine his chest and report your findings.

Recognition

There may be *reduced chest movement* on the affected side, associated with *tracheal deviation* to the affected side. On the affected side *breath sounds are reduced* and *vocal resonance is increased* (Fig. 1.36).

Interpretation

Confirm the diagnosis

With collapse of a lobe, vocal resonance is not increased. Remember that large bullae in chronic obstructive pulmonary disease can resemble pneumothoraces radiographically.

What to do next – consider causes

Causes of pneumothorax are listed in Box 1.23.

Consider severity/decompensation/complications

Clinical assessment is unreliable at estimating pneumothorax size (Box 1.24).

Secondary spontaneous pneumothorax (SSP) is associated with a higher morbidity and mortality than primary spontaneous pneumothorax (PSP). Tell the examiners that you would be alert to the possibility of a tension pneumothorax.

Consider function

Determine how limited the patient is by breathlessness.

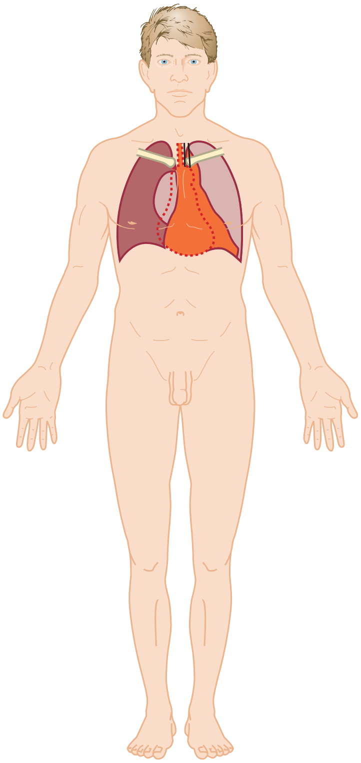


Figure 1.36 Pneumothorax.

Box 1.23 Causes of pneumothorax

Primary spontaneous pneumothorax (PSP)

- Often young adults, tall, who are smokers – subpleural blebs are thought to contribute to the development of PSP; the gradient in pleural pressure increases from base to apex, and alveoli in tall people are subject to higher distending pressures and, theoretically, development of subpleural blebs; subpleural blebs or bullae are more common in smokers

Secondary spontaneous pneumothorax (SSP)

- Lung disease, e.g. asthma / chronic obstructive pulmonary disease, pneumonia, cystic fibrosis, lung cancer, human immunodeficiency virus infection, cystic / nodular lung diseases
- Marfan's syndrome
- Catamenial (associated with menstruation)

Traumatic pneumothorax

- Iatrogenic (lines, mechanical ventilation)
- Trauma
- Mechanical ventilation

Tension pneumothorax

- Any pneumothorax may become a tension pneumothorax (air flow through a 'one-way' valve into the pleural space causes rapid cardiorespiratory compromise demanding immediate drainage)

Box 1.24 Pneumothorax size

The differentiation of a 'large' from a 'small' pneumothorax continues to be the presence of a visible rim of more than 2 cm between the lung margin and the chest wall (at the level of the hilum). Accurate pneumothorax size calculations are best achieved by CT scanning. A 2 cm rim of air equates to 50% of the hemithorax). However, management should be dictated more by symptoms than by size.

Discussion

How is a pneumothorax diagnosed?

Erect chest radiographs in inspiration are recommended for initial diagnosis. A small pneumothorax may not be immediately apparent and CT scanning is recommended for uncertain or complex cases and may be necessary to differentiate a pneumothorax from complex bullous disease, when aberrant tube placement is suspected or when surgical emphysema obscures the lung fields on chest X-ray.

What are the principles of managing a pneumothorax?

- Symptoms in PSP may be minimal or absent. In contrast, symptoms are greater in SSP, even if the pneumothorax is relatively small in size. The presence of breathlessness influences the management strategy, the size of a pneumothorax being less important than the degree of clinical compromise. Severe symptoms and signs of respiratory distress suggest the presence of tension pneumothorax.
- Strong emphasis should be placed on smoking cessation, to minimise the risk of recurrence. Pneumothorax is not usually associated with physical exertion.
- Patients with pre-existing lung disease tolerate a pneumothorax less well, and the distinction between PSP and SSP should be made at the time of diagnosis to guide appropriate management. Breathlessness indicates the need for active intervention, whilst the size of pneumothorax determines the rate of resolution, and is a relative indication for active intervention. Patients with PSP or SSP and significant breathlessness associated with any size of pneumothorax should undergo active intervention.
- Chest drains are required for patients with tension or bilateral pneumothorax or those with haemodynamic instability, who should be admitted to hospital.
- A management algorithm for spontaneous pneumothorax is given in Figure 1.37.

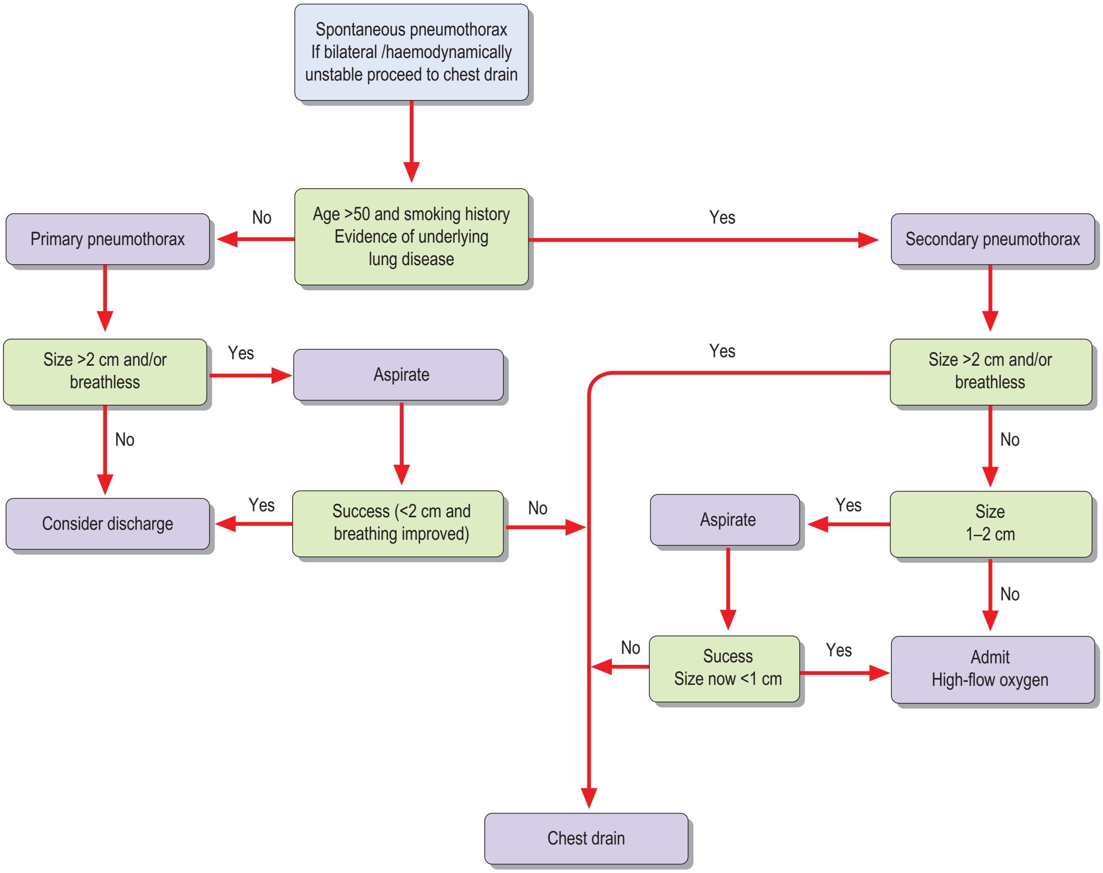

Spontaneous pneumothorax
If bilateral /haemodynamically unstable proceed to chest drain
Age >50 and smoking history
Evidence of underlying lung disease
No
Primary pneumothorax
Yes
Secondary pneumothorax
Size >2 cm and/or breathless
Yes
Aspirate
No
Consider discharge
Yes
Success (<2 cm and breathing improved)
No
Yes
Size >2 cm and/or breathless
No
Aspirate
Yes
Size 1–2 cm
No
No
Sucess
Size now <1 cm
Yes
Admit
High-flow oxygen
Chest drain

Figure 1.37 Pneumothorax management algorithm.

How is PSP managed?

- Observation is the treatment of choice for small PSP, without significant breathlessness. Patients with small PSP, without breathlessness, should be considered for discharge with early outpatient review, and should also receive clear advice to return in the event of worsening breathlessness.
- Selected, asymptomatic patients with a large PSP may be managed by observation alone.
- Needle (14–16 G) aspiration is as effective as large-bore (> 20 F) chest drains, and may be associated with reduced hospitalisation and length of stay. Following failed needle aspiration, small-bore (< 14 F) chest drain insertion is recommended. Referral to a respiratory physician should be made within 24 hours of admission and complex drain management is best effected in areas where specialist medical and nursing expertise is available.

How is SSP managed?

- All patients with SSP should be admitted to hospital for at least 24 hours, and receive supplemental oxygen. Most will require the insertion of a small-bore chest drain. All will require early referral to a chest physician.
- Those with a persistent air leak (common with SSP) should be discussed with a thoracic surgeon at 48 hours. Medical pleurodesis may be appropriate for inoperable patients.

What do you know about safe management of chest drains?

- The area of safety for intercostal drain insertion is between the third and fifth intercostal spaces in the mid-axillary line.
- Small-bore chest drains should normally be used but may not be suitable in the presence of pleural fluid (where they could block) or a large or persistent air leak (owing to inadequate re-expansion).
- Suction should not be routinely employed and only considered with high-volume, low-pressure systems to limit development of re-expansion pulmonary oedema.

- Chest drains should never be clamped if bubbling, and seldom even when not bubbling. A clamp should be removed immediately in a patient who becomes breathless or who develops surgical emphysema.

What about discharge and follow-up?

Patients should be advised to return to hospital if increasing breathlessness develops. All should be followed up by a respiratory physician until full resolution. Air travel should be avoided until full resolution. Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and a normal chest CT scan postoperatively.

When is medical chemical pleurodesis considered?

Chemical pleurodesis can control difficult or recurrent pneumothoraces but, since surgical options are more effective, it should be used only if a patient is either unwilling or unable to undergo surgery.

When should referral to thoracic surgeons be considered?

In cases of persistent air leak or failure of the lung to re-expand, an early (3–5 days) thoracic surgical opinion should be sought.

What surgical options are there?

Open thoracotomy and pleurectomy is the procedure with the lowest recurrence rate (approximately 1%) for difficult or recurrent pneumothoraces. Video-assisted thoracoscopic surgery (VATS) with pleurectomy and pleural abrasion is better tolerated, but has a higher recurrence rate of approximately 5%. Surgical chemical pleurodesis is best achieved by using 5 g sterile graded talc, with which the complications of acute respiratory distress syndrome and empyema are rare.

How is tension pneumothorax managed?

Tension pneumothorax is a medical emergency that requires heightened awareness in a specific range of clinical situations. Treatment is with oxygen and emergency needle decompression. A standard cannula may be insufficiently long if used in the second intercostal space.

What do you know about pneumothorax and pregnancy?

Pneumothorax recurrence is more common in pregnancy, poses risks to the mother and fetus, and requires close cooperation between chest physicians, obstetricians and thoracic surgeons. Simple observation and aspiration are usually effective, with elective assisted delivery and regional anaesthesia at or near term. A corrective surgical procedure (VATS) should be considered after delivery.

What do you know about catamenial pneumothorax?

Catamenial pneumothorax is underdiagnosed in women with pneumothorax. A combination of surgical intervention and hormonal manipulation requires cooperation with thoracic surgeons and gynaecologists.

CASE 1.24 OBSTRUCTIVE SLEEP APNOEA–HYPOPNOEA SYNDROME

Instruction

This 34-year-old woman was recently involved in a road traffic accident. Please examine her and discuss your findings and management.

Recognition

There may be *plethora*. The patient is *overweight*. Consider underlying causes, e.g. obesity, acromegaly, Cushing's syndrome (Fig. 1.38). Tell the examiners that you would wish to know the body mass index.

Interpretation

Confirm the diagnosis

Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) refers to recurrent episodes of complete or partial airway obstruction during sleep. Apnoea is defined by cessation of air flow for > 10 seconds with continued respiratory effort; hypopnoea refers to reduction, rather than cessation, of air flow. OSAHS is common, affecting at least 4% of men and 2% of women, yet around 80% is undiagnosed.

Tell the examiners you would ask about symptoms suggesting OSAHS (Boxes 1.25 and 1.26) and ask if continuous positive airway pressure (CPAP) is used at night.

Headaches appear to be no more prevalent in OSAHS than in the general population.

Box 1.25 **STOP–BANG criteria for risk of obstructive sleep apnoea–hypopnoea syndrome**

- Snoring (loud – audible in next room)
- Tiredness (daytime)
- Observed apnoea
- Pressure (raised blood pressure)
- Body mass index > 35
- Age > 50
- Neck circumference > 40 cm
- Gender male

≥ 3 criteria = high risk (though this encompasses a broad proportion of the population!)

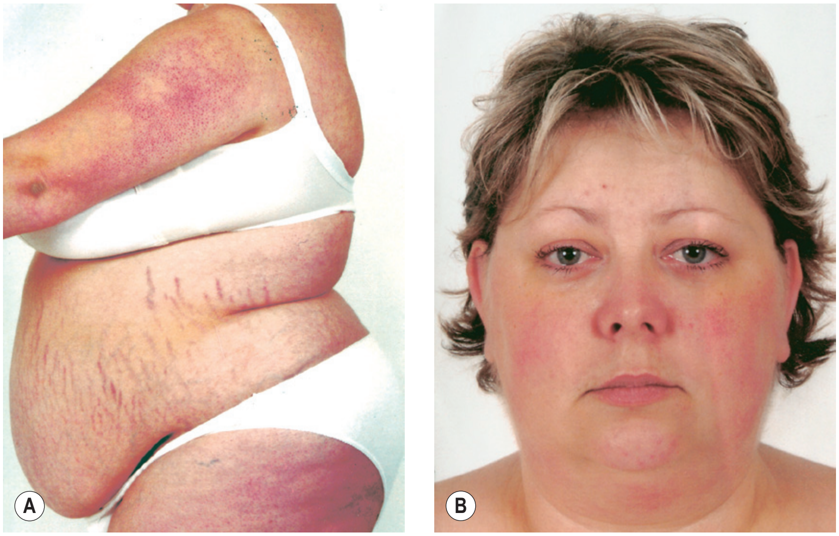


Figure 1.38 Cushing's disease.

Box 1.26 **Symptoms suggesting obstructive sleep apnoea–hypopnoea syndrome (OSAHS)**

- Excessive daytime sleepiness (measured by the Epworth score, a score > 10 is abnormal; the score correlates with the amount of sleep fragmentation rather than nocturnal hypoxia because apnoeic episodes – demonstrated by electroencephalography – are associated with arousal and impede entry into deeper phases of refreshing sleep; partial collapse of the pharynx may also occur in the absence of apnoea, sufficient to disrupt sleep – restlessness, choking or reflux-like symptoms – but not trigger hypoxia)
- Unrefreshing sleep
- Low mood
- Marital disharmony – snoring and personality changes (under-recognised and misinterpreted as depression)
- Memory loss (one night's sleep loss can produce 40% short-term memory loss); sleep-replete people also recall positive themes whilst those who are sleep deprived have a much more negative view of the world, perhaps alert to threats
- Increased pain susceptibility
- Nocturia (probably due to atrial natriuretic peptide release in response to pressure against a closed glottis); nocturia degree relates to OSAHS severity
- Impotence (rapid eye movement sleep disruption; dream sleep is associated with sexual arousal, tumescence and testosterone release)
- Unexplained absences
- Coma

What to do next – consider causes

Causes include pharyngeal crowding, nasal obstruction and other craniofacial predisposing features; heavy snoring can lead to a reddened and oedematous uvula and soft palate. Though commonly associated with an increased BMI, it is important to remember that 30% of patients are slim (these people may have abnormal tonsils or jaw retrognathia or a family history of an abnormal airway). Heavy goods vehicle drivers and American footballers (large neck) are at increased risk. Secondary medical causes include acromegaly, hypothyroidism, polycystic ovarian syndrome and drugs including testosterone. OSAHS risk increases with menopause.

Consider severity / decompensation / complications

- Increased cardiovascular disease risk (hypertension, ischaemic heart disease, atrial fibrillation, cerebrovascular disease, metabolic syndrome).
- Cor pulmonale is associated with OSAHS with chronic obstructive pulmonary disease (COPD); look for ankle swelling.
- Type 2 respiratory failure occurs with very severe nocturnal hypoventilation; obesity-related respiratory failure encompasses the entities of severe obstructive sleep apnoea with associated hypercapnia, lone obesity hypoventilation syndrome and combined obstructive sleep apnoea and obesity hypoventilation syndrome.
- Increased risk of road traffic accidents.

Consider function

OSAHS has major effects on quality of life, not attributable just to poor sleep but also to effects on personality and interactions with the world. Tell the examiners you would ask about:

- Impaired cognition (OSAHS particularly affects sustained attention and vigilance, information-processing speed, and visual and psychomotor performance or reaction times)

- Mood
- Effects on relationships.

Discussion

What is the place of a sleep study?

Full polysomnography, which includes detailed recordings of electroencephalography and electromyography, oximetry, oronasal air flow, respiratory effort and snoring, has been the gold standard. In practice more limited nocturnal recording is sufficient for diagnosis. Oximetry alone is insufficient because of the high false-negative rate (in patients with partial obstruction but without hypoxia) and the high false-positive rate (in patients with coexisting lung disease such as COPD). Snoring per se is insufficient evidence for OSAHS and not an indication for a sleep study. An additional symptom, such as daytime somnolence, nocturnal choking or witnessed apnoeas, is an indication.

What management options are available for obstructive sleep apnoea?

OSAHS is treatable. General measures include weight reduction, smoking cessation and alcohol reduction. An ENT opinion may be sought if nasopharyngeal pathology is contributory. CPAP is the most effective treatment. Mild OSAHS may occur only lying on the back; treatment here would ideally include lying on the side, but the problem is we cannot easily determine the positions of our sleep, which are unrelated to the positions we go to sleep and wake up in.

CASE 1.25 LUNG TRANSPLANT

Instruction

Please examine this woman's chest and report your findings.

Recognition

There is *evidence of major surgery for a presumed severe chronic lung condition*. There is *no breathlessness or tachypnoea*. There is a *mid-sternotomy scar*. Chest expansion is symmetrical and normal and percussion, breath sounds and vocal resonance are normal (Fig. 1.39).

Interpretation

Confirm the diagnosis

Tell the examiners you would ask the patient!

What to do next – consider causes

List some reasons to the examiners for lung transplantation (Box 1.27). Heart and lung transplant is performed in some conditions.

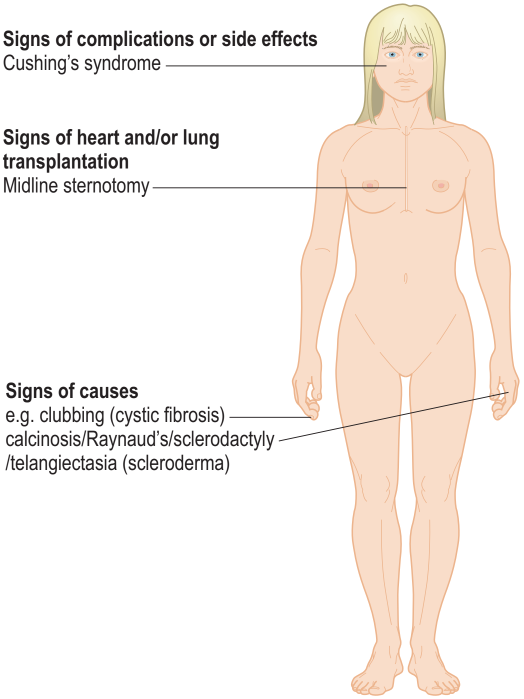

Signs of complications or side effects
Cushing's syndrome
Signs of heart and/or lung transplantation
Midline sternotomy
Signs of causes
e.g. clubbing (cystic fibrosis)
calcinosis/Raynaud's/sclerodactyly /telangiectasia (scleroderma)

Figure 1.39 Lung transplantation.

Box 1.27 Indications for lung transplantation

- Cystic fibrosis and suppurative lung disease
- Obstructive lung disease, e.g. emphysema with or without α1-antitrypsin deficiency
- Restrictive lung disease, e.g. idiopathic pulmonary fibrosis, fibrosis secondary to connective tissue disease, chronic allergic alveolitis and sarcoidosis
- Pulmonary vascular disease, especially idiopathic pulmonary arterial hypertension and congenital heart disease
- Rare diseases, e.g. Langerhans cell granulomatosis and lymphangioleiomyomatosis

Consider severity / decompensation / complications

Mention some common complications, e.g. surgical graft problems, graft rejection, infection and side effects of immunosuppression.

Consider function

Tell the examiners you would explore pre- and post-transplantation quality of life.

Discussion

Is rejection common in lung transplantation?

Most patients have one or two episodes of acute rejection within the first few months.

What do you know about bronchiolitis obliterans syndrome?

This is a difficult complication of lung transplantation with rapidly progressive lung degeneration, irreversible airway obstruction and high mortality despite continuous oxygen therapy and enhanced immunosuppression. Symptoms include cough, dyspnoea and malaise. This is an entirely different entity from bronchiolitis obliterans organising pneumonia (now termed cryptogenic organising pneumonia) (Case 1.13), which is a fibrotic lung condition with a good prognosis on corticosteroid treatment.

Abdominal system

Examination of the abdominal system

Inspection

General

- The patient should be lying comfortably supine, one pillow supporting the head, arms rested at the sides, exposed from xiphisternum to pubic symphysis.
- Introduce yourself, ensure that the patient is comfortable and then stand back.
- Note any cachexia.

Skin

- Look at the skin, especially for jaundice, pallor or pigmentation. Some skin signs of gastrointestinal disease are given in Table 1.28.

Face

- Look at the face, notably the sclera for jaundice, the eyelids for xanthelasmata (primary biliary cirrhosis) and the mouth for telangiectasia, pigmentation or signs of Crohn's disease.

Trunk

- Look for gynaecomastia and spider naevi.

Table 1.28 Some skin signs of gastrointestinal pathology

Sign	Description	Disease
Jaundice	Yellow sclera and skin	Liver disease
Anaemia	Pallor	Liver disease Gastrointestinal blood loss Malabsorption (iron, B12 or folate deficiency)
Pigmentation	Slate grey (haemosiderin stimulating melanin production by melanocytes)	Haemochromatosis
	Freckle-like macules around mouth and on buccal mucosa, fingers and toes	Peutz–Jegher syndrome (associated with hamartomatous polyps, bleeding, and rarely gastrointestinal adenocarcinoma)
	Addisonian-like pigmentation	Addison's disease Malabsorption
	Acanthosis nigricans (brown or black velvety papules due to confluent axillary papillomas)	Diabetes mellitus Rarely associated with gastrointestinal adenocarcinoma
Telangiectasia	Telangiectasia of lips and mouth	Hereditary haemorrhagic telangiectasia
	Telangiectasia and sclerodactyly	Scleroderma
Other	Erythema nodosum	Inflammatory bowel disease
	Pyoderma gangrenosum	Inflammatory bowel disease
	Clubbing	Inflammatory bowel disease
	Mouth ulcers	Inflammatory bowel disease
	Fragile vesicles	Porphyria cutanea tarda (associated with liver disease)
	Flushing	Carcinoid syndrome
	Red, scaly lesions	Zinc deficiency (nutritional deficiencies cause various rashes)

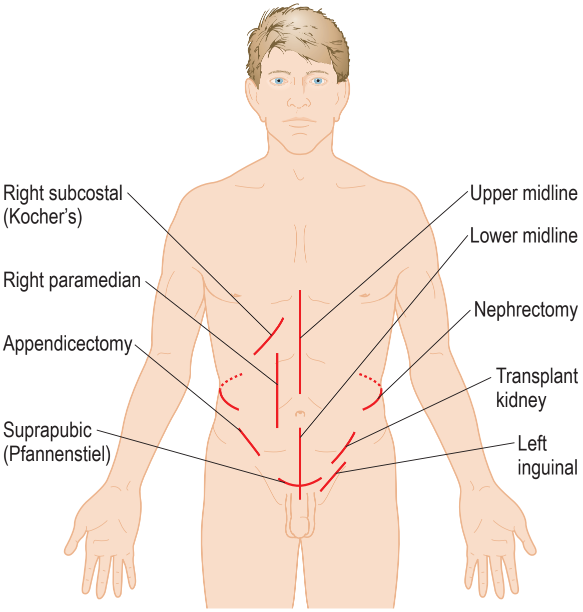

Right subcostal (Kocher's)
Right paramedian
Appendicectomy
Suprapubic (Pfannenstiel)
Upper midline
Lower midline
Nephrectomy
Transplant kidney
Left inguinal

Figure 1.40 Abdominal scars.

Hands

- Look for other signs of chronic liver disease (Case 1.26) and feel for a flap (better felt than observed).

Abdomen

- Look for scars (Fig. 1.40).
- Look for localised or generalised swellings.
- Look for abnormal pulsation (visible pulsation of the abdominal aorta is normal in thin people).
- Look for distended veins. Caput medusa refers to veins radiating from the umbilicus (Fig. 1.41) and suggests portal hypertension leading to portal-to-systemic flow via the umbilical veins. In inferior vena cava obstruction, collateral veins open up to channel blood to the heart (Fig. 1.41).

Palpation

Initial palpation

- Ask if there is any pain or tenderness.
- Palpate with your arm at the level of the patient's abdomen. With the palmar aspect of the fingers of your right hand (fingers flexed gently at the metacarpophalangeal joints, finger pads rather than tips making contact), palpate the four quadrants or nine regions of the abdomen (Fig. 1.42) for masses. Gentle, superficial palpation often yields more than deeper palpation. Palpate more deeply to detect deeper masses and define any masses. Guarding with rigidity and rebound tenderness is a sign of peritonitis and should not appear in PACES. Palpate

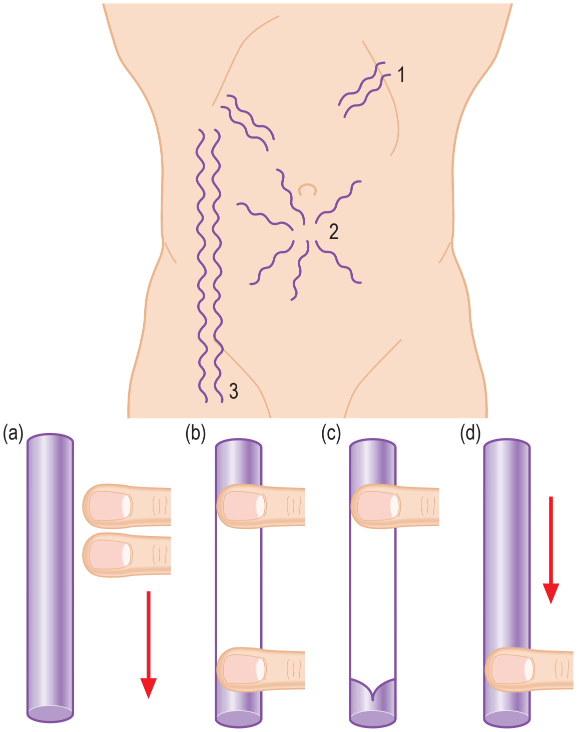


Figure 1.41 Prominent abdominal wall veins: 1, thin veins at the costal margin (normal); 2, caput medusae (rare); 3, inferior vena caval obstruction. Detecting the direction of flow of a vein: (a) place two fingers firmly on the vein; (b) move the second finger to empty it and keep it occluded; (c) the second finger is removed but the vein does not refill; (d) at repeat testing and removing the first finger, filling occurs indicating the direction of flow. Below the umbilicus: in caput medusae, flow is towards the legs; in inferior vena cava obstruction, flow is towards the head.

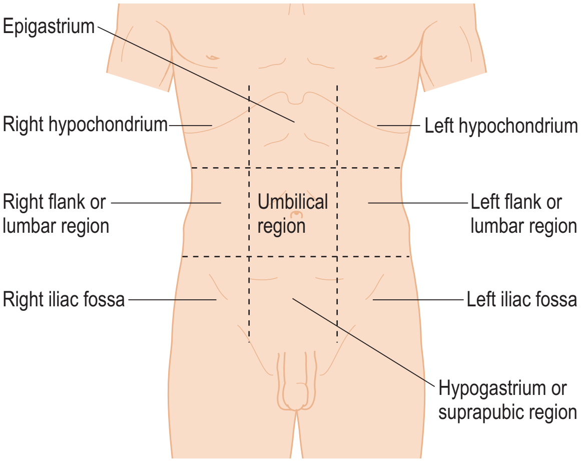

Epigastrium
Right hypochondrium
Left hypochondrium
Right flank or lumbar region
Umbilical region
Left flank or lumbar region
Right iliac fossa
Left iliac fossa
Hypogastrium or suprapubic region

Figure 1.42 Regions of the abdomen.

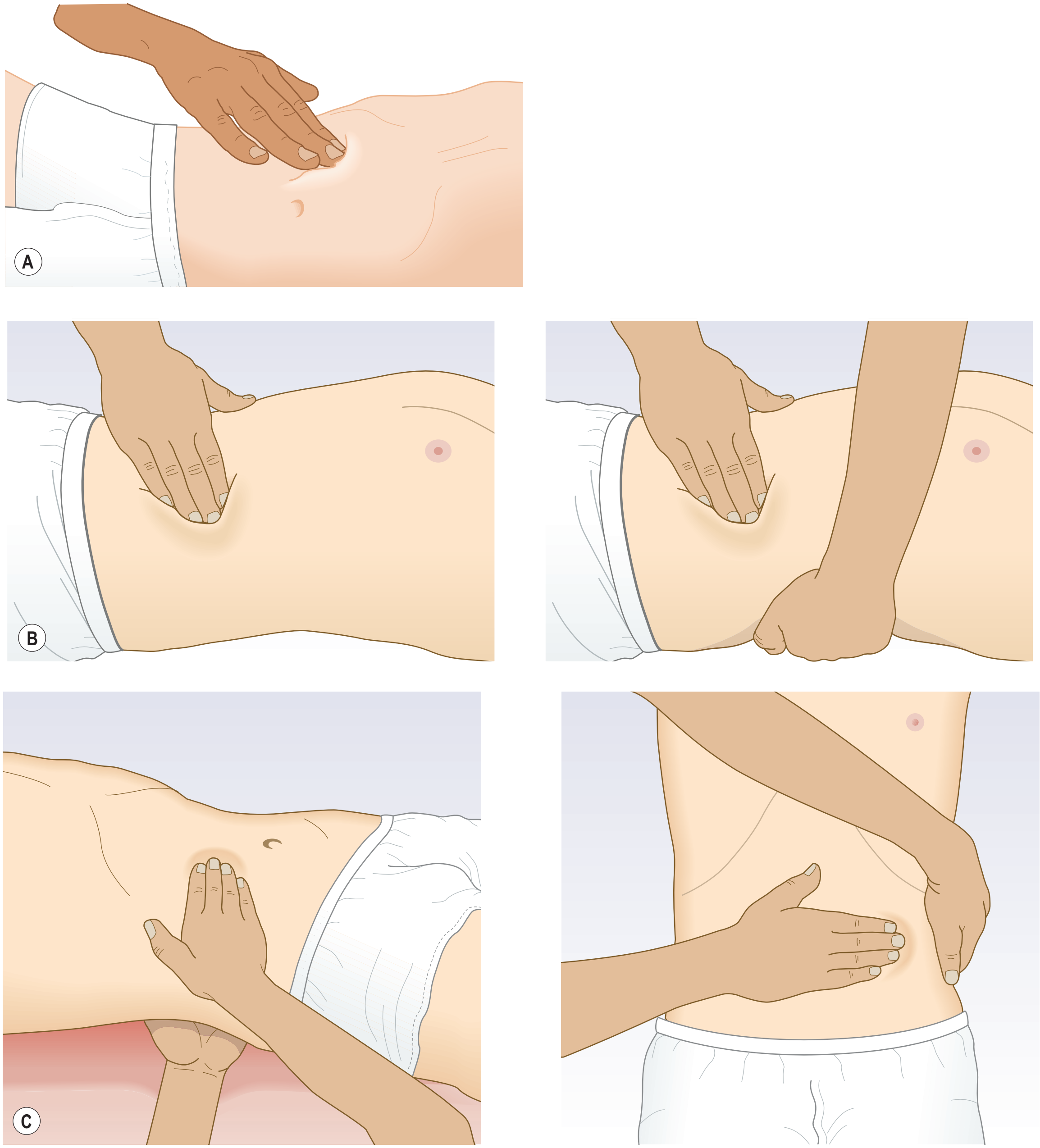


Figure 1.43 (A–C) Palpation for abdominal organomegaly. *(Part B from Douglas, G., Nicol, F., Robertson, C., 2009. Macleod's Clinical Examination, Twelveth ed. with permission.)*

specifically for liver, splenic or kidney enlargement (Fig. 1.43).

Liver

- Start palpation at the right iliac fossa so as not to miss a massively enlarged liver. An enlarging liver enlarges downwards. Use the radial border of your index finger or finger pads. A normal liver may be palpable 2 cm below the costal margin. The liver displaces downwards on deep inspiration to meet your fingers. Keep your fingers stationary as the patient breathes in to feel its downward movement. If you feel the liver edge lower than expected,

determine whether it is displaced downwards (hyperinflated lungs) or enlarged through percussion (below). Measure enlargement in centimetres from the costal margin. Remember that Riedel's lobe is a promontory of the right lobe's inferior aspect that very infrequently extends as far as the right iliac fossa.
- If you detect a liver edge, note its surface and edge (smooth or irregular), whether or not it is tender and whether or not it is pulsatile.

Spleen

- The spleen is not normally palpable and generally must be one and a half to twice normal size to be palpable. Start at the right iliac fossa as an enlarging spleen enlarges towards the right iliac fossa. Rolling the patient onto the right side may detect mild to moderate splenomegaly. Bimanual palpation of the spleen is preferred, although the purpose of the left hand is more to steady the patient than feel the spleen, which is protected largely by the ribs posterolaterally.

Kidneys

- Palpate for these bimanually and by ballottement. Ballottement refers to a 'flicking' movement in which the lower hand, in the renal angle, pushes the kidney towards the upper hand anteriorly. The kidneys are normally palpable only in thin subjects. They move with respiration and may appear resonant because of overlying bowel. A common dilemma is in distinguishing a large left kidney from splenomegaly (Table 1.29).

Masses

- Attempt to describe any mass with respect to site, size, shape, surface, edge, consistency (hard or soft), fixation or mobility (with respect to the skin), tenderness and pulsatility. Normal and abnormal masses sometimes found are listed in Box 1.28.

Table 1.29 Distinguishing a large left kidney from a large spleen

	Spleen	Kidney
Upper border	Not palpable	Palpable (you can 'get above it')
Medial notch	Yes	No
Movement with inspiration	Downward and medially	Downward only
Ballotable	No	Yes (because of retroperitoneal position)
Percussion	Dull over spleen	Often resonant over kidney

Percussion

Percussion over liver and spleen

- Percuss from the right iliac fossa towards the liver. The level of the upper border varies with the phase of respiration but when percussing along the right lateral chest wall the lower three or four ribs are dull to percussion with a normal liver. Normal span should be less than 12.5 cm when percussing along the mid-clavicular line (from around the sixth rib superiorly to the lower edge inferiorly) but there is notorious observer error and measurement is not mandatory in PACES.
- Percuss from the right iliac fossa towards the spleen.

Examining for ascites

- Percuss for shifting dullness if you suspect ascites because of generalised abdominal distension – fat, flatus, faeces, fluid or fetus. First confirm ascites by percussing from the umbilicus, which is resonant unless ascites is massive and tense, to the flanks, which are stony dull (Fig. 1.44A and B). Secondly ask the patient to roll onto their left side whilst marking (or keeping your finger over) the resonant–dull interface. Fluid from the right side further fills the left flank and the area of dullness on the left extends towards the umbilicus but on the right percussion becomes resonant (Fig. 1.44C).
- In patients with large-volume ascites, a fluid thrill may be elicited by tapping one flank and feeling transmission of the fluid wave to the other. An assistant's hand on the centre of the abdomen limits transmission of the wave through the abdominal wall.

Box 1.28 **Normal and abnormal masses**

Normal masses

- Liver edge (including a large Riedel's lobe or the left lobe)
- Kidneys
- Aorta
- Rectus abdominis
- Hard faeces
- Distended bladder
- Small inguinal lymph nodes

Abnormal masses

- Carcinoma of sigmoid colon (left iliac fossa)/caecum (right iliac fossa)
- Carcinoma of stomach or pancreas (epigastrium)
- Secondary lymphadenopathy or lymphoma (hard, often bulky masses arising at any site)
- Abscesses, e.g. appendiceal, diverticular, psoas
- Inflammatory masses, e.g. Crohn's disease
- Ovarian cysts or tumours
- Abdominal aortic aneurysm (pulsatile and, if leaking, may be expansile)

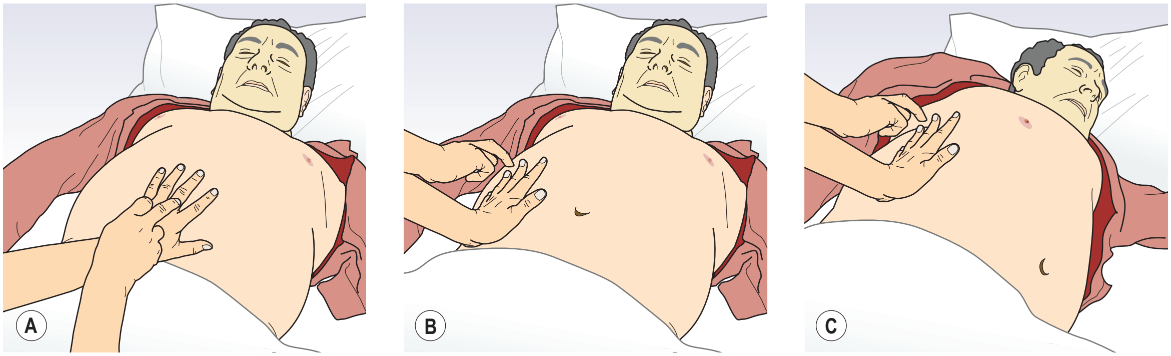


Figure 1.44 Percussing for shifting dullness. *(From Douglas, G., Nicol, F., Robertson, C., 2009 Macleod's Clinical Examination, Twelveth ed. with permission.)*

Auscultation

- Auscultate for bowel sounds, bruits (renal bruits are often heard over the epigastrium), a venous hum (rare, but almost pathognomonic of portal hypertension) and friction rubs (exceedingly rare, caused by inflamed peritoneal surfaces).

Completion of abdominal examination

- Palpate for lymph nodes. Completion of examination includes, not to be performed in PACES, examination of the hernial orifices, genitalia and rectum.

Summary

A summary of the abdominal system examination sequence is in the Summary box.

SUMMARY BOX – ABDOMINAL SYSTEM EXAMINATION SEQUENCE

- From a distance look for bedside clues.
- Look for cachexia.
- Look at the skin for jaundice, pallor or pigmentation.
- Look at the face for jaundice, xanthelasmata, telangiectasia, pigmentation or mouth ulcers.
- Look at the trunk for gynaecomastia and spider naevi.
- Look at the hands for signs of chronic liver disease.
- Look at the abdomen for scars, swellings, pulsation or distended veins.
- Gently palpate all regions of the abdomen.
- Feel for an enlarged liver, starting at the right iliac fossa and noting its downward displacement with inspiration; note its size and surface characteristics.
- Feel for an enlarged spleen, starting at the right iliac fossa.
- Bimanually palpate the kidneys.
- Feel for masses.
- Percuss over the liver and spleen.
- Examine for shifting dullness +/− the fluid thrill of ascites.
- Listen for bowel sounds and bruits.

Cases

CASE 1.26 CHRONIC LIVER DISEASE

Instruction

Please examine this patient's abdominal system. Discuss your findings and comment on possible causes.

Recognition

There are many signs of chronic liver disease (CLD). It may be useful to group these into three categories (Fig. 1.45). Palmar erythema and spider naevi are shown in Figures 1.46 and 1.47, respectively.

Interpretation

Confirm the diagnosis

Spider naevi offer the best initial confirmation of CLD.

What to do next – consider causes

These are listed in Box 1.29 and Figure 1.45. The epidemic of heavy alcohol consumption in the UK is reflected in the rising rates of alcoholic liver disease, alcohol being the leading cause of cirrhosis and more than 80% of liver-related deaths in the UK being due to cirrhosis secondary to alcohol.

Tell the examiners you would ask about:

- Alcohol intake
- Previous jaundice, transfusions or drug use (viral hepatitis)
- Medications, including complementary therapies
- Family history (genetic haemochromatosis, Wilson's disease, α_1-antitrypsin deficiency)
- Occupational history
- Travel history
- Sexual history (viral hepatitis).

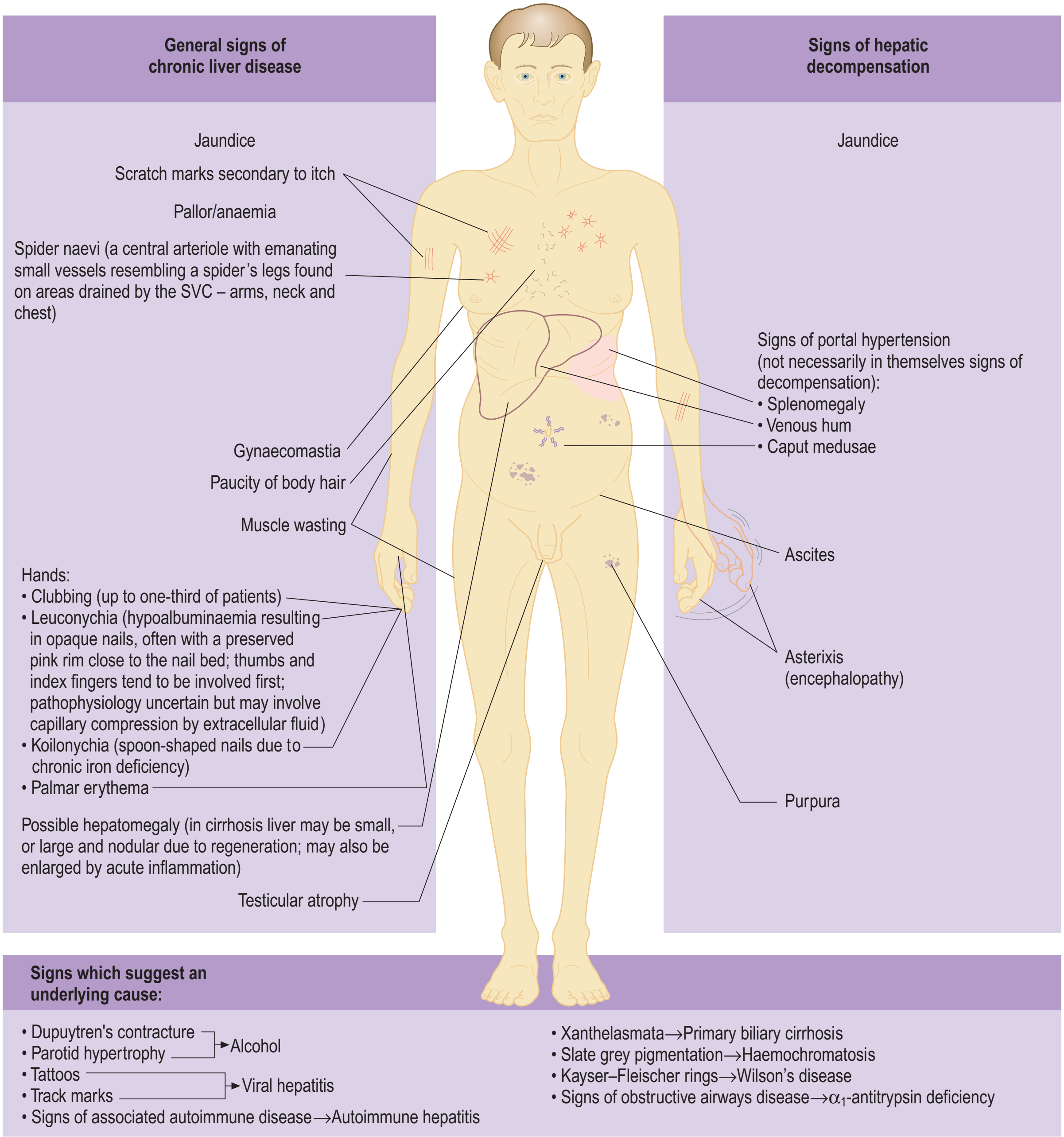

General signs of chronic liver disease
Jaundice
Scratch marks secondary to itch
Pallor/anaemia
Spider naevi (a central arteriole with emanating small vessels resembling a spider's legs found on areas drained by the SVC – arms, neck and chest)
Gynaecomastia
Paucity of body hair
Muscle wasting
Hands:
• Clubbing (up to one-third of patients)
• Leuconychia (hypoalbuminaemia resulting in opaque nails, often with a preserved pink rim close to the nail bed; thumbs and index fingers tend to be involved first; pathophysiology uncertain but may involve capillary compression by extracellular fluid)
• Koilonychia (spoon-shaped nails due to chronic iron deficiency)
• Palmar erythema
Possible hepatomegaly (in cirrhosis liver may be small, or large and nodular due to regeneration; may also be enlarged by acute inflammation)
Testicular atrophy
Signs of hepatic decompensation
Jaundice
Signs of portal hypertension (not necessarily in themselves signs of decompensation):
• Splenomegaly
• Venous hum
• Caput medusae
Ascites
Asterixis (encephalopathy)
Purpura
Signs which suggest an underlying cause:
• Dupuytren's contracture
• Parotid hypertrophy
→Alcohol
• Tattoos
• Track marks
→Viral hepatitis
• Signs of associated autoimmune disease→Autoimmune hepatitis
• Xanthelasmata→Primary biliary cirrhosis
• Slate grey pigmentation→Haemochromatosis
• Kayser–Fleischer rings→Wilson's disease
• Signs of obstructive airways disease→α_1-antitrypsin deficiency

Figure 1.45 Possible signs in chronic liver disease. SVC, superior vena cava.

Consider severity / decompensation / complications

Severity as a determinant of prognosis

Prognosis correlates with the severity of hyperbilirubinaemia, hypoalbuminaemia (g/l), prothrombin time prolongation, ascites, encephalopathy, renal disease, shock or anaemia and comorbidity, notably sepsis. Tell the examiners that the Child–Pugh score (Table 1.30) or the UK model of end-stage liver disease (MELD) score (Box 1.30) may be used to determine functional status and severity, and have prognostic relevance.

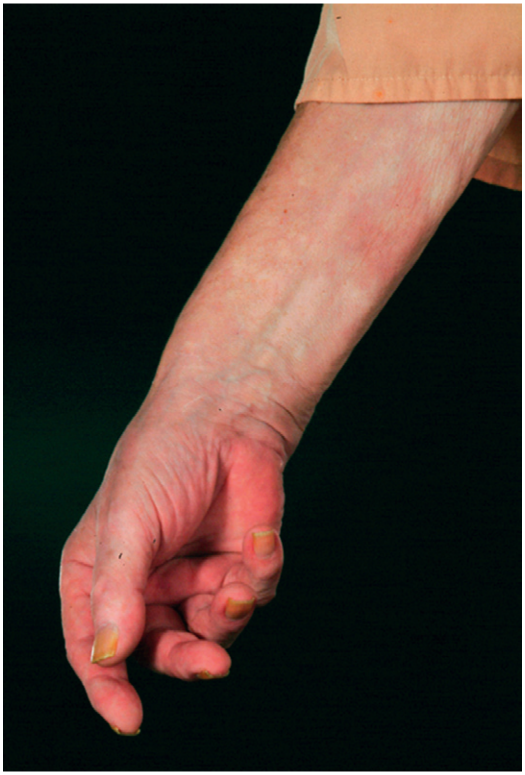


Figure 1.46 Palmar erythema.

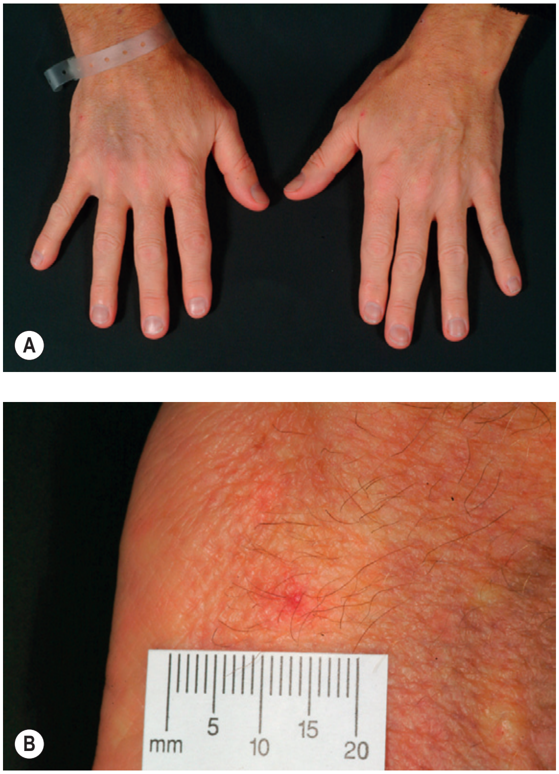


Figure 1.47 Spider naevi.

Box 1.29 **Causes of cirrhosis**

- Alcohol
- Hepatitis B
- Hepatitis C
- Chronic autoimmune hepatitis
- Primary biliary cirrhosis
- Sclerosing cholangitis
- Haemochromatosis
- Wilson's disease
- Non-alcoholic steatohepatitis
- α_1-antitrypsin deficiency
- Chronic Budd–Chiari syndrome

Table 1.30 Child–Pugh score

	1 point	2 points	3 points
Bilirubin (μmol / l)	< 34	34–51	> 51
Albumin (g / l)	> 35	28–35	< 28
Prothrombin time (seconds prolonged)	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy grade	None	1–2	3–4

Advantages of the MELD score include a measure of renal function, and removal of subjective measurements for ascites and encephalopathy.

Hepatic decompensation

Signs of hepatic decompensation are described in Table 1.31.

Hepatocellular carcinoma (HCC)

This can be a long-term complication of cirrhosis of any cause.

Consider function

Well-being relates to both severity of disease and the underlying cause.

Discussion

What do you understand by the terms hepatic failure and hepatic decompensation?

Histologically, the liver is made up of lobules, each containing a central hepatic vein, a peripheral portal 'triad' comprising bile duct and branches of portal vein and hepatic artery, and hepatocytes between the two. Functionally, the liver comprises acini, centred on the portal triad. The zone around the central vein sustains injury in venous congestion, as in right heart failure, while in hepatitis and cirrhosis damage starts at the portal triads.

The liver is a factory whose purpose is to metabolise carbohydrate, fat and protein. While liver enzymes are useful in assessing causes of jaundice, serum bilirubin, albumin and prothrombin time better reflect synthetic liver function.

Most hepatic insults bring the threat of necrosis and failure of liver function or hepatocellular failure. The end result of a wide range of causes, from causes of fulminant and acute liver damage to causes of CLD, are similar: decompensation of liver function. The extraordinary capacity for hepatic regeneration must be overcome for this to occur. Jaundice is common in acute hepatitis because the speed of onset does not allow time for regeneration, but tends to occur only in CLD, either when reserve is exhausted or when acute damage compromises pre-existing limited reserve.

Box 1.30 **Model of end-stage liver disease (MELD) score**

MELD score is given by:

$$3.8\ (\ln \text{serum bilirubin mg/dl}) + 11.2\ (\ln \text{INR}) + 9.6\ (\ln \text{serum creatinine mg/dl}) + 6.4$$

where: ln is the natural logarithm; INR is international normalised ratio.

Any score < 1.0 is set to 1.0.

MELD scores between 6 and 40 are considered for transplant allocation in the USA.

With transjugular intrahepatic portosystemic shunting (TIPSS) the best outcomes may be with scores < 14, with poor outcomes > 24.

What do you understand by the terms chronic liver disease (CLD) and cirrhosis?

CLD is increasingly common. The natural history of liver injury is fibrosis in response to hepatocellular injury, which is usually asymptomatic until decompensation occurs. Until this point, elevated liver enzymes are the only indicators of disease. Clinical stigmata of CLD are not present in the absence of severe fibrotic liver disease. Thorough investigation of abnormal liver function tests is thus essential for diagnosis at a stage where underlying disease is likely to be treatable. Cirrhosis is the diffuse process of fibrosis and regenerative nodule formation and can be the end result of many insults; the response of the liver to such insults is recurrent activation of an acute pro-inflammatory immune response with chronic progression to fibrosis mediated by fibrogenic cytokines and repair. The stages of cirrhosis (by no means always a sequence) are liver cell necrosis, inflammation, fibrosis and nodular regeneration. Cirrhosis starts at the portal triads, rippling outwards to form bridges of necrosis that progress to fibrosis and fibrous bands termed septae. In advanced disease there is more fibrosis than regenerated liver. Regenerating liver grows between septae, and the septa–regeneration junction is called the limiting plate. Tightly compacted septal bands with small islands of regeneration equate to micronodular cirrhosis; macronodular cirrhosis involves larger islands of regeneration. In short, cirrhosis is characterised by extensive fibrosis, resulting in architectural distortion with nodule formation, leading to portal hypertension and end-stage liver disease (ESLD).

How does portal hypertension arise?

The portal vein enters the liver at the porta hepatis and sends a branch to each lobe. It receives blood from all veins draining the abdominal part of the gastrointestinal

Table 1.31 Hepatic decompensation

Feature	Signs
Jaundice	Yellow sclera and skin
Portal hypertension (a complication of chronic liver disease, decompensated if there is variceal bleeding or hepatorenal syndrome)	Splenomegaly (but size correlates poorly with portal pressure) Secondary hypersplenism (can cause peripheral blood cytopenias) Caput medusae (distended veins radiating from the umbilicus) Venous hum
Ascites	Shifting dullness Fluid thrill
Hepatic encephalopathy	The clinical picture is complex and may be classified by the West Haven criteria into four grades: Grade 1: Subtle loss of awareness, reduced attention, impaired addition or subtraction Grade 2: Apathy, disorientation in time or place, behavioural change Grade 3: Somnolence but responsive to stimuli, confusion, gross disorientation Grade 4: Coma
Coagulopathy	Purpura and bleeding

tract and is formed from the union of the superior mesenteric and splenic veins. Normal portal flow rate is about 1–1.5 l/min with a pressure of 5–10 mmHg. When flow is obstructed, either from within or outside the liver, collateral circulation develops to carry blood into systemic veins (portosystemic shunting, although cyanosis occasionally occurs in liver disease as a result of pulmonary venous shunts). Two problems then arise: the liver's metabolic function is bypassed and increasing pressure in collaterals (termed *varices*) causes bleeding. Varices are commonly oesophageal, derived from the left gastric vein; there are multiple layers of veins in the oesophagus and varices usually develop in the deep intrinsic layer. They occur at other sites including the stomach, colon and rectum. Hyperdynamic circulation accompanies portal hypertension and may in part develop to maintain portal flow as collaterals lower the pressure.

What are the causes of portal hypertension?

These may be:

- Prehepatic, e.g. portal vein thrombosis, extrinsic compression
- Hepatic, e.g. cirrhosis, acute hepatitis, congenital hepatic fibrosis
- Posthepatic, e.g. Budd–Chiari syndrome, constrictive pericarditis.

What is Budd–Chiari syndrome?

This refers to hepatic vein thrombosis giving rise to ascites, hepatomegaly and pain. It may be acute and fulminant, or chronic. A thrombophilic disorder underlies most cases. Ascitic fluid has high protein content and a liver biopsy often shows centrilobar necrosis and sinusoidal congestion. Treatment is by shunting in a specialist centre (it can induce hepatic failure) and transplantation if that fails. Thrombolytic therapy is ineffective because the clot is not usually recent, but long-term anticoagulation is indicated.

What is the most important complication of portal hypertension?

Portal hypertension is a major complication of cirrhosis, although portal hypertension and its signs such as caput medusae and splenomegaly do not in themselves imply hepatic decompensation. Variceal bleeding is the most important complication of portal hypertension, representing decompensation.

What are the causes of bleeding in liver disease?

These are listed in Box 1.31.

What is meant by acute-on-chronic liver failure (ACLF)?

ACLF is defined as an acute deterioration in liver function over a period of 2–4 weeks, usually associated with a precipitating event, leading to a severe deterioration in clinical status with jaundice and hepatic encephalopathy (HE) and/or hepatorenal syndrome (HRS). It is often complicated by multiple organ failure and associated with a poor prognosis.

Box 1.31 **Causes of bleeding in liver disease**

- Coagulopathy – prolonged prothrombin time owing to impaired synthesis of prothrombin and other coagulation factors (II, VII, IX, X)
- Thrombocytopenia due to splenomegaly and hypersplenism
- Portal venous bleeding in portal hypertension
- Gastritis and peptic ulceration associated with alcohol-induced liver disease

What precipitates ACLF?

Patients with cirrhosis may develop liver failure either from chronic disease progression or secondary to an acute precipitant (ACLF) and inflammation seems to play a key role in pathogenesis. The precipitant may be variceal bleeding, sepsis, ischaemia or direct liver injury relating to alcohol, hepatotoxic drugs or viral hepatitis.

How does ACLF present?

Patients with ACLF may present in a number of ways.

Variceal bleeding

These develop as a consequence of portal hypertension. A hepatic venous pressure gradient greater than 12 mmHg is strongly associated with a risk of variceal bleeding. The risk of variceal bleeding can be estimated by the size of varices, the presence of endoscopic red signs and the degree of liver dysfunction. Variceal bleeding may present with large or initially small volume haematemesis, melaena or rectal bleeding and often significant haemodynamic compromise. Patients with known varices may not be tachycardic if on beta blockers.

Ascites

This occurs as a result of portal hypertension and salt and fluid retention resulting from stimulation of the renin–angiotensin system; the contribution from the reduced oncotic pressure of hypoalbuminaemia is less significant.

Hepatorenal syndrome (HRS)

This is a functional disorder in which renal failure (serum creatinine > 133 μmol/l) develops in the context of advanced liver failure, ascites and structurally normal kidneys. Whilst an oversimplification, the sequence of events are cirrhosis, portal hypertension, splanchnic vasodilation, reduced effective arterial blood volume, activation of vasoconstrictor mechanisms and renal vasoconstriction leading to HRS. HRS is associated with a poor prognosis and represents a late stage of ESLD. HRS may be classified into two types: type I with a 50% reduction in creatinine clearance to < 20 ml/min within 2 weeks and associated with a worse prognosis, and type II HRS with a more chronic onset.

Hepatic encephalopathy (HE)

HE is a neurocognitive disorder associated with both acute and chronic liver injury. It spans a spectrum of impairment from normal performance through to coma and development is often unpredictable. HE may be low grade at presentation with mild confusion, reversed sleep cycle or asterixis, whilst high-grade encephalopathy presents with a Glasgow Coma Score of 8 or below. In acute liver failure, the central role of ammonia from impaired protein metabolism in the development of brain oedema remains incontrovertible but precipitating factors – such as inflammation, infection, variceal haemorrhage, sedating drugs, constipation, alcohol and electrolyte disturbances, notably hyponatraemia, catabolic states such as surgery or trauma, transjugular intrahepatic portosystemic shunting – modulate the pathophysiological effects, particularly in patients with cirrhosis. That metabolic changes account for HE is supported by a tendency for reversibility. Coagulopathy-related intracerebral bleeding should also be considered.

Other features of hepatic synthetic dysfunction

Coaguloapathy promotes bleeding. A systemic inflammatory response syndrome is common. Patients with cirrhosis are immunocompromised and sepsis is common, often occult. There should be a low threshold for considering spontaneous bacterial peritonitis (SBP), 50% of which is asymptomatic and may be complicated by HRS.

Which investigations are important in ACLF?

Laboratory

The chief prognostic laboratory parameters are prothrombin time, bilirubin, creatinine and albumin as these are markers of hepatic synthetic function. Transaminases, gamma-glutamyl transferase and alkaline phosphatase may provide information about the nature of liver injury. Alcoholic hepatitis often presents with an aspartate aminotransferase to alanine aminotransferase ratio above 2. A full blood count may demonstrate thrombocytopenia and leucopenia, features of hypersplenism and thus portal hypertension. Blood cultures should be taken.

If the patient is presenting *de novo*, a non-invasive liver screen should be requested (Box 1.32).

Diagnostic ascitic tap

Patients with ACLF and ascites should undergo a diagnostic ascetic tap. A polymorphonuclear cell count greater than 250 cells/mm^3 is diagnostic of SBP. The most common organism is a Gram-negative single enteral bacterial species. Mixed growth suggests perforation.

Imaging

Abdominal ultrasound imaging can help confirm features of CLD, and with Doppler assessment of hepatic and portal vein patency exclude an acute Budd–Chiari syndrome and portal vein thrombosis.

Box 1.32 **Non-invasive liver screen**

- Viral serology – immunoglobulin M (IgM) anti-hepatitis A antibody, hepatitis B surface antigen, IgM anti-hepatitis B core antibody, anti-hepatitis C antibody, anti-hepatitis E antibody
- Antinuclear antibody, smooth muscle antibody, LKM-1 antibody, immunoglobulins (autoimmune hepatitis)
- Antimitochondrial antibody (primary biliary cirrhosis)
- Ferritin, transferrin saturation (haemochromatosis)
- Caeruloplasmin (Wilson's disease)
- α_1-antitrypsin levels (α_1-antitrypsin deficiency)
- Lipid profile, fasting glucose
- Alphafetoprotein

What are the important aspects of management of ACLF?

Variceal bleeding

Management is outlined in Table 1.32. Varices bleed from the lower 5 cm of the oesophagus because of high pressure, and so are explosive rather than erosive, and anaesthetic support can be very important. The rebleeding rate is 70% and only modestly correlates with severity of liver dysfunction.

Ascites (including SBP)

Patients with features of ACLF or pyrexia in the context of ascites need a diagnostic ascitic tap and broad-spectrum antibiotics such as a third-generation cephalosporin. In 30% of cases SBP will be complicated by HRS, although studies have demonstrated that this can be reduced with administration of salt-poor human albumin solution. Therapeutic paracentesis should be deferred in an acute presentation of SBP, again because of the risk of renal failure. Once ascites develops, all patients should be considered for liver transplantation since the long-term prognosis is poor. Patients should start modest salt restriction, and spironolactone as the first-line diuretic drug. Patients with alcoholic liver disease need to stop drinking.

Hepatorenal syndrome (HRS)

Patients with HRS have a high mortality. In cirrhosis, serum creatinine underestimates the degree of renal impairment and renal failure should be managed with particular care. Patients with HRS have features of salt and fluid overload and are hyponatraemic. They should be rendered euvolaemic and, once achieved, may require low-dose terlipressin to maintain an adequate urine output. HRS commonly complicates SBP and there should be a low threshold for intravenous antibiotics. Pentoxifylline may have a role in alcoholic hepatitis complicated by HRS.

Table 1.32 Management of varices

Primary prevention of bleeding	All patients with large varices, and those with cirrhosis and severe liver disease, irrespective of the size of varices, should be given primary prophylaxis with non-selective beta blockers. These reduce variceal pressure by reducing cardiac output (blocking β_1) and allowing unopposed splanchnic vasoconstriction (blocking β_2); there is no additional benefit when combined with banding in primary prevention of bleeding but beta blockers may prevent recurrence of varices. There is no evidence for pre-primary prophylaxis.
	Endoscopic variceal ligation (banding) is equivalent and used if there are contraindications or intolerance to beta blockers.
Management of acutely bleeding varices	Resuscitation Patients require a high-dependency environment. Airway management is vital as aspiration risk is high. Large-bore or central access should be established. Volume resuscitation with fluid, blood and blood product support is a priority. The aim is to transfuse to a haemoglobin of 10 g / dl and correct coagulopathy. Overfilling exerts pressure on varices and may worsen bleeding; saline may aggravate ascites and dextrose is favoured. Intravenous vitamin K 10 mg should be given, but is unlikely to influence coagulation status in the initial period; fresh frozen plasma may be indicated.
	Pharmacological therapy Vasoactive drugs that cause splanchnic vasoconstriction, and thus reduce portal pressure, play a key role in stabilising variceal bleeding. Drugs include terlipressin, somatostatin and octreotide. Terlipressin, a derivative of vasopressin, is highly effective, controlling active variceal bleeding in 75–80% of cases at 48 hours without endoscopic therapy and the only drug shown to improve survival, and may be renoprotective. It is associated with a small risk of coronary and peripheral arterial vasospasm and arrhythmias, and warrants cardiac monitoring. Therapy (e.g. terlipressin 2 mg i.v. 6-hourly) should be continued for 2–5 days.
	Endoscopic therapy Any cirrhotic patient with upper gastrointestinal (GI) bleeding (however stable on presentation) should undergo early upper GI endoscopy. Endoscopic treatment options include variceal ligation ('banding') and sclerotherapy (injection of sclerosant into a bleeding varix or overlying mucosa, the former obliterating the varix lumen by thrombosis, the latter inducing inflammation and fibrosis for bleeding oesophageal varices). Variceal ligation is superior to sclerotherapy in both safety and efficacy when combined with vasoactive drugs. Gastric varices are a greater endoscopic challenge and options include histoacryl 'glue' or thrombin injection. Patients in whom haemostasis is not achieved require Sengstaken tube placement and consideration of transjugular intrahepatic portosystemic shunt (TIPSS) placement (balloon tamponade can control bleeding in up to 90% of patients when exsanguination seems likely but cannot be applied for more than 12 hours because of mucosal ischaemia).
	Transjugular intrahepatic portosystemic shunt (TIPSS) TIPSS insertion is used as salvage therapy for variceal bleeding refractory to endoscopic therapy. By shunting blood from the portal to the hepatic vein pressure is reduced as is the risk of variceal bleeding. A transjugular approach is used, the hepatic vein cannulated, the portal vein punctured and a shunt deployed from the hepatic to the portal vein. If the resultant hepatic vein portal gradient is less than 12 mmHg the risk of variceal bleeding is significantly reduced. Once portal access is established, variceal coil embolisation can be achieved. TIPSS insertion produces haemostasis in 90% of endoscopic refractory patients. TIPSS-related complications include encephalopathy, pulmonary hypertension and worsening liver function. Patients with variceal haemorrhage and TIPSS *in situ* should undergo Doppler studies to assess shunt patency.
	Surgery The need for surgery is rare, and surgical portosystemic shunts are associated with a high risk of encephalopathy and mortality.
	Antibiotics Broad-spectrum antibiotics should be given to reduce the risk of sepsis, an independent prognostic factor of failure to control bleeding or early rebleeding.
Secondary prevention	Secondary prophylaxis of variceal bleeding is mandatory with combined beta blockers and early endoscopic ligation.

Hepatic encephalopathy (HE)

Potential precipitants should be identified and treated. Existing therapies include lactulose, and newer therapies such as rifaximin may abrogate systemic inflammation in patients with, or at risk of developing, HE. The probability of transplant-free survival after a first episode of HE at 3 years is only 23% and referral for liver transplantation should be considered early. A high-protein diet may be detrimental in terms of HE risk but is important for overall health.

Other therapies

Coagulopathy should be corrected with vitamin K. Intravenous albumin seldom has a role but two clear indications are in SBP to prevent renal failure and as volume replacement in high-volume paracentesis. Nutritional support from a dietitian is important, as is glycaemic control, especially in alcoholic and diabetic patients, and failure of gluconeogenesis is a feature of end-stage liver failure.

Alcoholic hepatitis is an important cause of ACLF and Maddrey's discriminant factor (DF = prothrombin time − control (seconds) × 4.6 + (bilirubin (μmmol) / 17) where a DF > 32 indicates possible benefit, or the Glasgow alcoholic hepatitis score can be calculated to give an estimate of the potential benefit of steroid therapy. Steroids can also play a role in a flare of autoimmune liver disease. Histological confirmation is often required and the risk of sepsis with steroids should be considered. Patients with an alcohol history should be prescribed Pabrinex, oral thiamine and B vitamins, and intravenous vitamin K. ACLF due to hepatitis B can be managed with low-dose lamivudine but antiviral therapy plays no role in the acute setting in patients with hepatitis C. Artificial and bioartificial liver support systems are a key area of research, particularly in ACLF.

What is the prognosis in ACLF?

Mortality from a first-presentation variceal bleed is about 50% and heavily influenced by the severity of underlying liver disease. Child–Pugh class is a good predictor of survival. Patients with SBP have an in-hospital mortality of 20%, survival being heavily influenced by the presence or absence of HRS. Once patients develop SBP, cumulative recurrence rates are 70% with a median survival of 9 months. Patients with type I HRS have a prognosis of less than 2 weeks, with fewer than 10% surviving their hospital admission.

What is meant by acute liver failure (ALF)?

ALF is characterised by jaundice, coagulopathy and encephalopathy in patients with previously normal liver function. The time to onset of jaundice and / or encephalopathy is used to classify patients into the following groups:

- Hyperacute liver failure: less than 7 days
- ALF: 7–28 days
- Subacute liver failure: 5–12 weeks.

ALF is associated with multiple organ failure and a poor prognosis.

What are the causes of ALF?

The main causes of ALF are viral hepatitis (e.g. hepatitis A, acute hepatitis B, endemic hepatitis E) or drug-induced hepatitis. Wilson's disease, autoimmune hepatitis and ischaemic hepatitis (liver enzymes levels often extremely high) may also cause ALF. Drug-induced liver injury may be a direct toxic effect or an immunological reaction to either the drug or an active metabolite. Drugs can cause a diverse array of liver injury, either acute or chronic. Adaptation, with only a transient increase in liver function, can occur. There is marked geographic variation in responsible agents: in the West paracetamol, non-steroidal anti-inflammatory drugs, antibiotics, anticonvulsants, disease-modifying agents in rheumatic diseases, psychotropics and recreational drugs are the most common offending agents, whereas, in Asia, herbal and dietary supplements are more common.

How does ALF present?

The time interval to onset of liver failure is important. Patients with hyperacute liver failure are more likely to present with HE and haemodynamic compromise. Patients with subacute liver failure are less likely to develop encephalopathy and may even have ascites. A thorough history, particularly for prescribed and non-prescribed medication, is important. It is important to ascertain any features that suggest CLD. The possibility of acute fatty liver of pregnancy in women in the third trimester of pregnancy should be considered because it is thought to be part of a spectrum with the HELLP (hepatic encephalopathy, liver abnormalities, low platelets) syndrome and pre-eclampsia.

What investigations are important in ALF?

These include:

- Paracetamol / salicylate levels
- Epstein–Barr serology
- Hepatitis B serology
- Cytomegalovirus serology
- Varicella-zoster virus serology
- Hepatitis A / E serology.

Key parameters should be monitored regularly, in particular prothrombin time, bilirubin, creatinine, pH and presence of encephalopathy as these have prognostic relevance; pH is of particular prognostic importance in paracetamol toxicity. A routine non-invasive liver screen should be processed early with urgent imaging of the liver and hepatic and portal vessels. A transjugular liver biopsy may be required. Intrinsic liver enzymes are less prognostic, and tend to be very high in hepatitis from ischaemia, and sometimes in infective hepatitis and autoimmune hepatitis, but lower in alcohol hepatitis.

Box 1.33 **Possible indications for liver transplantation**

Chronic liver disease

- Alcohol-related liver disease
- Chronic hepatitis B or C virus infection
- Malignancy (e.g. hepatocellular carcinoma)
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Biliary cirrhosis (usually primary; secondary; e.g. cystic fibrosis)
- Haemochromatosis
- Wilson's disease
- α_1-antitrypsin deficiency
- Sclerosing cholangitis
- Granulomatous liver disease, e.g. sarcoidosis
- Storage diseases
- Chronic Budd–Chiari syndrome
- Cryptogenic cirrhosis

Acute liver failure (King's College Hospital criteria)

Paracetamol

- pH < 7.3, irrespective of degree of encephalopathy; prothrombin time > 100 s; serum creatinine > 300 µmol / l if grade III/IV encephalopathy

Non-paracetamol

- Prothrombin time > 100 s regardless of degree of encephalopathy, or any three of the following–aetiology: non-A, non-B, idiosyncratic drug reactions, halothane hepatitis; age < 10 or > 40 years; interval from jaundice to encephalopathy > 7 days; prothrombin time > 50 s; bilirubin > 300 µmol / l

Miscellaneous (with or without chronic liver disease)

- Polycystic liver disease
- Portopulmonary hypertension
- Intractable portal hypertensive bleeding
- Recurrent cholangitis
- Intractable cholestatic pruritus
- Surgical gene therapy (e.g. primary oxalosis, familial amyloidosis, familial hypercholesterolaemia)

What are the important aspects of management of ALF?

Patients with ALF should be managed in a high-dependency, specialist area and discussed with a liver transplant unit, and investigations and clinical assessment continued at frequent intervals until recovery or transfer to a transplant unit. Encephalopathy is a particular concern. Empirical antibacterial and antifungal cover is often given and there should be a low threshold for *N*-acetylcysteine to cover the possibility of paracetamol toxicity. Criteria for referral to a specialist centre in paracetamol hepatotoxicity are:

- Day 2: arterial pH ≤ 7.3, international normalised ratio (INR) > 3, encephalopathy, creatinine (Cr) > 200, hypoglycaemia
- Day 3: arterial pH ≤ 7.3, INR > 4.5, encephalopathy, Cr > 200
- Day 4: any rise in INR, encephalopathy, Cr > 250.

What is the prognosis in ALF?

Subacute liver failure is associated with a worse prognosis; patients with ALF and hyperacute liver failure have higher rates of spontaneous recovery. Liver transplantation remains the only effective treatment.

Which patients with liver disease may be suitable for liver transplantation?

Where the benefits of transplantation outweigh the risks of surgery and are likely to improve prognosis, indications for transplantation are listed in Box 1.33. Long-term outcome is now good.

Box 1.34 **Investigating asymptomatic abnormal liver function tests (LFTs)**

Asymptomatic abnormal LFTs are common, affecting 8% of the population. The commonest causes are alcoholic and non-alcoholic fatty liver disease (NAFLD). NAFLD is the absolute commonest cause of elevated liver enzymes, whereas alcohol is the commonest cause of death from cirrhosis and its complications. Asymptomatic abnormal LFTs may be transient and should be repeated after weight reduction or cessation of alcohol or potentially hepatotoxic drugs. The history may exclude non-hepatic causes as well as potential hepatic causes. Abnormal LFTs in patients taking statins are common and are more likely to be caused by coexistent NAFLD. Investigations aim to identify patients with progressive liver disease, since cirrhosis can be clinically silent in early stages. Concurrent clinical hepatomegaly, thrombocytopenia and splenomegaly all warrant further investigation to exclude cirrhosis. An ultrasound scan and a serological chronic liver disease screen remain the standard investigations.

How should asymptomatic abnormal liver function tests be investigated?

An approach is outlined in Box 1.34.

What is the role of liver biopsy in investigating liver disease?

Liver biopsy still has an important role in diagnosis, but non-invasive markers can differentiate mild fibrosis from cirrhosis. Evaluation of morphology can also inform clinical management, e.g. when assessing severity in chronic viral hepatitis. Where dual pathology is suspected, histological assessment may help identify the main cause. Liver biopsy sometimes reveals abnormalities (e.g. iron overload, α_1-antitrypsin globules) not detected by previous investigations.

CASE 1.27 JAUNDICE

Instruction

Please look at this patient's skin and examine his/her abdomen. Discuss your findings.

Recognition

Jaundice is present. (Jaundice is most apparent in fluid/tissues with high protein concentration such as cerebrospinal/ocular fluid and elastic tissue – skin, sclera (Fig. 1.48), blood vessel walls.)

Interpretation

Confirm the diagnosis

Jaundice may reflect acute liver disease or chronic liver disease (CLD). Look for signs of CLD.

What to do next – consider causes

Tell the examiners that the history might suggest a cause of CLD (Case 1.26) and that jaundice may be prehepatic, hepatic or cholestatic (Table 1.33).

Consider severity/decompensation/complications

Look for other signs of hepatic decompensation (Case 1.26) and tell the examiners you would aim to determine the severity of liver disease (Case 1.26).

Consider function

Well-being relates to both severity of disease and the underlying cause.

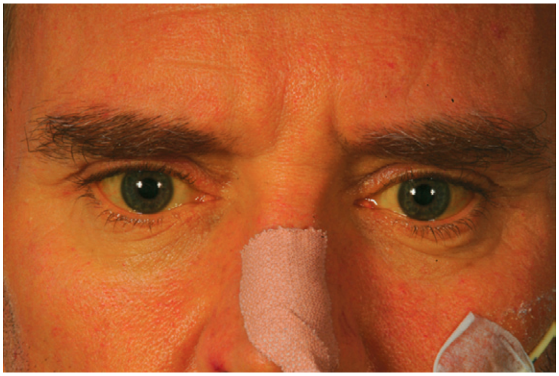


Figure 1.48 Jaundice.

Discussion

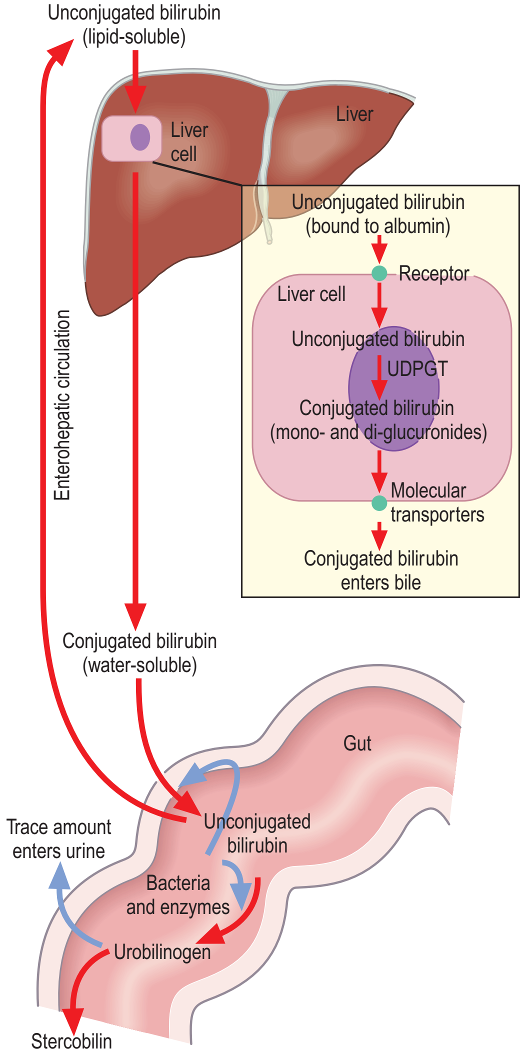
What is jaundice?

Jaundice refers to the yellow skin discoloration resulting from excess bilirubin in the blood (> 34–50 µmol/l). Conjugated hyperbilirubinaemia tends to produce more intense jaundice because of its water solubility.

Summarise bilirubin metabolism and excretion pertinent to understanding how jaundice arises

Bilirubin metabolism is summarised in Figure 1.49.

Normally 500–600 ml of bile is produced and secreted daily, a golden-red colour; 40% is secreted from



Unconjugated bilirubin
(lipid-soluble)
Liver
Liver cell
Unconjugated bilirubin
(bound to albumin)
Receptor
Liver cell
Unconjugated bilirubin
UDPGT
Conjugated bilirubin
(mono- and di-glucuronides)
Molecular transporters
Conjugated bilirubin enters bile
Enterohepatic circulation
Conjugated bilirubin
(water-soluble)
Gut
Unconjugated bilirubin
Trace amount enters urine
Bacteria and enzymes
Urobilinogen
Stercobilin

Figure 1.49 Bilirubin metabolic pathway and jaundice. UDPGT, uridine diphosphate glucuronyltransferase.

Table 1.33 Causes of jaundice

	What to do	What it is	Causes	Further assessment
Prehepatic	Look for anaemia	Excess bilirubin load on hepatocytes	Usually haemolysis Massive transfusion Haematoma resorption Ineffective erythropoiesis Inherited disorders of bilirubin metabolism	Anaemia without overt bleeding and normal liver enzymes and synthetic function tests Elevated reticulocyte count Haemolysis on blood film Haptoglobins Unconjugated hyperbilirubinaemia
Hepatic (hepatocellular)	Look for signs of chronic liver disease	Failure of liver cell to take up, metabolise (conjugate) or excrete bilirubin	Acute / fulminant liver failure Acute-on-chronic liver disease Chronic liver disease / cirrhosis and decompenation (e.g. hepatitis from alcohol, drugs, viral hepatitis, autoimmune liver disease, primary bilairy cirrhosis, primary sclerosing cholangitis) Intrahepatic cholestasis (sepsis, drugs, total parenteral nutrition, viral)	Unconjugated and conjugated hyperbilirubinaemia Transaminase rise more pronounced than alkaline phosphatase rise; may be very high in acute hepatitis on a background of a normal liver, but low in cirrhosis where fewer hepatocytes remain to be destroyed Deranged synthetic liver function Liver 'screen' for causes of chronic liver disease
Posthepatic (cholestatic)	Look for cachexia Tell the examiners you would ask about symptoms with fatty meals	Defective transport of bilirubin by biliary duct system becuse of obstruction to flow (intra- or extrahepatic) or damage to intraheptic bile ducts	Cholelithiasis (gallstones in common bile duct) Cholangitis (sepsis) Carcinoma of pancreas (head, ampulla) Cholangiocarcinoma Extrinsic compression (lymph nodes) Intrahepatic cholestasis (sepsis, drugs, total parenteral nutrition, viral) Systemic IgG4 disease / autoimmune pancreatitis	Conjugated hyperbilirubinaemia Alkaline phosphatase (and gamma-glutamyl transferase) rise more pronounced than transaminase rise

Frequently an insult causes a combination of hepatocellular failure and cholestasis (e.g. primary biliary cirrhosis) and the biochemical abnormalities in any of the above states may precede jaundice. Ig, immunoglobulin.

hepatocytes (liver cells) and 60% from cholangiocytes (biliary epithelial cells). Bile drains from the liver through bile ducts and into the duodenum at the duodenal papilla.

Bilirubin is a water-insoluble yellow pigment, the product of haem breakdown (75%) and other haem proteins (plus a little from ineffective bone marrow erythropoiesis). Free (unconjugated) bilirubin is bound to albumin, lipid soluble, and transported to liver cell receptors before entering the liver cell. Here it binds to cytoplasmic protein and is conjugated with uridine diphosphate glucuronic acid (UDPGA) by uridine diphosphate glucuronosyl transferase (UDPGT) from smooth endoplasmic reticulum. Different forms of UDPGT exist but UDPGT_1 is predominant; expression of the *UDPGT* gene sequence is promoted by a 'transcription promoter region' in a nearby exon containing the nucleotide sequence TATAA. Conjugation converts unconjugated bilirubin to conjugated bilirubin, largely bilirubin diglucuronide (releasing UDP), which is more water soluble than free bilirubin. Bilirubin diglucuronide is transported out of the cell across a concentration gradient and by molecular transporters into the bile canaliculi and into the gut. Thus total bilirubin comprises free (unconjugated) and conjugated bilirubin, the latter in smaller amounts overall.

The gut mucosa is relatively impermeable to conjugated bilirubin, which is hydrolysed back to unconjugated bilirubin and reduced to urobilinogen by gut bacterial enzymes that enable gut permeability. Therefore some unconjugated bilirubin enters the enterohepatic circulation and some forms urobilinogen. Some urobilinogen is reabsorbed into the general circulation, some ends up in the urine and some is passed into the stool as stercobilinogen where it is oxidised to stercobilin causing brown coloration.

Which types of bilirubin might be detected in the urine?

Normally bilirubin is not present in urine except as traces of urobilinogen. In unconjugated hyperbilirubinaemia or prehepatic jaundice (overuse of normal pathways) it is detectable as increased urobilinogen. In conjugated hyperbilirubinaemia (outflow to gut obstructed) it enters urine in its conjugated water-soluble form producing dark urine; the stools are pale because urobilinogen, and hence stercobilin, is absent.

What are the inherited disorders of bilirubin metabolism?

Gilbert's syndrome

Gilbert's syndrome is a common (2–5% of population), harmless, autosomal dominant defect of the TATAA box sequence – A(TA)6TAA changed to A(TA)7TAA – causing abnormal UDPGT$_1$ leading to 70% deficiency of bilirubin glucuronidation. It results in mild, intermittent unconjugated hyperbilirubinaemia (17–85 μmol/l), occasionally with mild jaundice. Episodes may be precipitated by stress, fasting or intercurrent infection. It does not give rise to other abnormalities in liver function. Reassurance is all that is needed. Types 1 and 2 Crigler–Najjar syndromes are very rare and severe autosomal recessive defects in which UDPGT is essentially absent.

Dubin–Johnson syndrome

Dubin–Johnson syndrome is a benign, autosomal recessive defect of molecular transporters (MRP-2 gene mutations) responsible for transporting conjugated bilirubin out of cells. It is common in the Middle East and Iranian Jews. It gives rise to conjugated hyperbilirubinaemia, without cholestasis symptoms or markers. Cholangiography contrast materials are not transported into the bile, and the liver is green-black at autopsy. Rotor syndrome shares the same biochemistry but with a good prognosis with no hepatic pigment and dye is excreted into the biliary tree.

How would you investigate cholestatic jaundice?

This starts with ultrasound scanning to determine whether or not the bile ducts are dilated. Dilated ducts suggest extrahepatic cholestasis. Normal ducts suggest intrahepatic cholestasis. Extrahepatic causes include gallstones, tumours, strictures and parasites. Intrahepatic causes include primary biliary cirrhosis, sclerosing cholangitis, sepsis and drugs. Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) is an appropriate next step for extrahepatic disease, and for intrahepatic disease a liver biopsy is appropriate.

What types of gallstone are there, how do they arise, and how are they managed?

There are three types: white cholesterol (80%), black calcium bilirubinate (15%) and brown pigment stones. They may sit within bile ducts or the gall bladder and are caused by stasis and infection in the biliary system. Stones form if bile is sequestered into the gall bladder at a greater rate than flow in the ducts can remove it. Supersaturation of bile with cholesterol (insoluble) heightens the problem with crsytal formation. Bacteria such as *Escherichia coli* and *Klebsiella* produce glucuronidase converting water-soluble conjugated bilirubin back to lipid-soluble / water-insoluble unconjugated bilirubin, a further reason for crystals developing. These and other 'nucleation' factors mean that stones can form within 2 days in susceptible patients that would ordinarily take 2 weeks of bile stasis.

Gallstones are common, but most are asymptomatic. Typical presentations include biliary colic and acute cholecystitis. Complications include empyema and mucocele of the gall bladder, acute pancreatitis and obstructive jaundice due to bile duct stones. Symptomatic stones are treated by laparoscopic cholecystectomy. Occasionally, empyema in an unfit patient is managed by percutaneous cholecystostomy. Cholangitis usually responds to biliary drainage by endoscopic sphincterotomy with or without stenting. Stones in the bile duct are removed by laparoscopic or open surgery, or endoscopic sphincterotomy. Obstructive jaundice is best treated by endoscopic sphincterotomy and stone extraction. If stones are large or impacted, a plastic pigtail stent can be inserted and in an unfit patient this may be serially changed as long-term management.

What do you know about cholangiocarcinoma (CC)?

This is usually adenocarcinoma of the ductular epithelium of the billiary tree; 25% is intraheptic within the liver, 50% is at the hilum, and 25% in the extrahaptic ducts. It is usually fatal because of late presentation and lack of treatment. Importantly, it is rapidly increasing in prevalence (10- or 12-fold in the West in the last 10 years), although some of this may be attributable to increased detection.

CASE 1.28 ASCITES

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *generalised swelling* (differential diagnosis fluid, fat, faeces, flatus, fetus) of the abdomen (Fig. 1.50) with

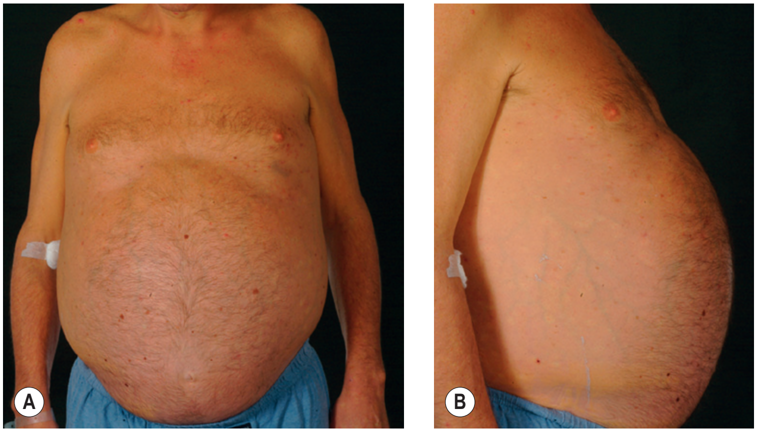


Figure 1.50 Ascites.

Table 1.34 Causes of ascites

Cause	What to do
Chronic liver disease	Look for signs of chronic liver disease (Case 1.26) Tell the examiners that the history might suggest a cause of chronic liver disease
Malignancy (especially gastric, ovarian and liver metastases, and peritoneal mesothelioma or metastases)	Look for cachexia
Right / biventricular failure	Look for a raised jugular venous pulse and peripheral oedema
Nephrotic syndrome	Tell the examiners you would check a urinalysis
Rare causes, e.g. hypothyroidism, constrictive pericarditis, Meig's syndrome, serositis in familial Mediterranean fever	Consider if other diagnoses are excluded

shifting dullness. There may be a *fluid thrill* in tense ascites, and the umbilicus may be everted. To palpate organs in the presence of ascites you must use a 'dipping' technique, pressing quickly, flexing at the wrist.

Interpretation

Confirm the diagnosis

Shifting dullness is pathognomonic.

What to do next – consider causes

These are listed in Table 1.34.

Consider severity / decompensation / complications

Look for other signs of hepatic decompensation (Case 1.26) and tell the examiners you would aim to determine the severity of liver disease (Case 1.26). Uncomplicated ascites that is not infected and not associated with hepatorenal syndrome may be classified as grade 1 (mild) only detectable by ultrasound, grade 2 (moderate) with moderate distension or grade 3 (large) with gross distension. Refractory ascites is that which cannot be shifted easily or which recurs rapidly.

Consider function

Well-being relates to both severity of disease and the underlying cause.

Discussion

What is the mechanism of ascites formation?

Over 75% of ascites is due to liver disease. The pathogenesis is uncertain but contributing factors include hypoalbuminaemia, portal hypertension and peripheral vasodilatation promoting sodium and water retention by stimulating the renin–angiotensin–aldosterone system.

What laboratory analysis would you request on ascitic fluid?

This should include a cell count and differential, protein, albumin and amylase concentration, cytology and Gram stain and culture. The macroscopic appearance of ascitic fluid is also important: straw coloured (most causes), turbid (pyogenic, TB), bloody (malignancy, TB), chylous (pancreatitis). In chronic liver disease, spontaneous bacterial peritonitis should be considered, diagnosed by paracentesis, with microscopy and culture and excess neutrophils. Ascites may be minimal and detectable only by ultrasound.

What is the value of the serum–ascites albumin gradient?

Most causes of ascites are transudates (< 25 g/dl), malignancy and peritoneal TB being notable exceptions. Because diuresis affects the total ascitic protein concentration, the serum–ascites albumin gradient (SAG) is sometimes a preferred method of characterising ascites. The SAG correlates directly with portal pressure. Patients with normal portal pressures have a gradient < 1.1g/dl. Conditions causing exudative ascites also tend to have a gradient < 1.1 g/dl, whereas ascites associated with heart failure, nephrotic syndrome or cirrhosis with portal hypertension usually has a gradient > 1.1 g/dl.

Is the chest X-ray ever abnormal as a consequence of ascites?

It may show a right pleural effusion because diaphragmatic channels open up and transmit fluid.

How would you manage ascites?

Any underlying remediable cause is identified and treated. Moderate ascites may be managed in the outpatient setting if without other complications of cirrhosis. Salt restriction and diuretics, especially the aldosterone antagonist spironolactone (50–200 mg daily), are important; the commonest reason for diuretic 'failure' is inadequate salt restriction: < 40–60 mmol (1–1.5 g) of salt daily is ideal but unpalatable and difficult to achieve, but < 80 mmol daily is practical. Weight loss of up to 500 g daily is desirable, and up to 1 kg daily if there is peripheral oedema. Therapeutic paracentesis may be necessary for tense ascites, with concurrent administration of albumin; albumin prevents paracentesis-induced circulatory dysfunction with risks of hypotension, recurrent ascites, hepatorenal syndrome and death, all more likely if more than 5 litres of fluid are removed.

CASE 1.29 ALCOHOLIC LIVER DISEASE

Instruction

Please examine this patient's abdominal system. You may briefly look for other signs you think may help determine an underlying cause. Discuss your findings and the likely cause.

Recognition

General *signs of chronic liver disease* may be present (Case 1.26) in this cachectic patient with signs of undernutrition.

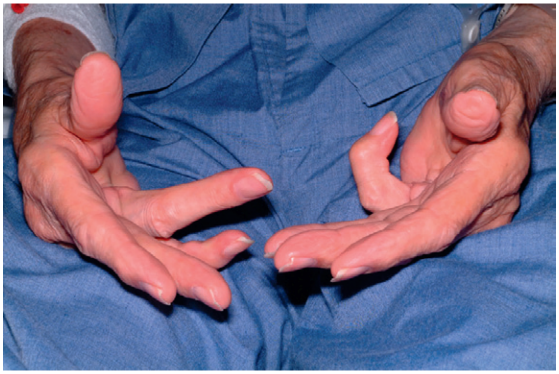


Figure 1.51 Dupuytren's contractures.

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about alcohol intake. Remember that two or more causes of chronic liver disease may coexist.

What to do next – consider causes / assess other systems

Tell the examiners that you would ask about alcohol consumption, previous jaundice, previous transfusions, drug use, occupation, travel and sexual history.

Dupuytren's contractures (Fig. 1.51, not always due to alcohol!) and *parotid enlargement* may be present (parotid enlargement is also a feature of sarcoidosis, Sjögren's syndrome and obstructed drainage). Other accompaniments to alcohol excess include cerebellar signs (*past pointing, broad-based gait*), Wernicke's encephalopathy (*ophthalmoplegia*) and evidence of dilated cardiomyopathy (*displaced apex +/− signs of heart failure*).

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26). Other complications of alcohol misuse are given in Box 1.35. Genetic polymorphisms probably account for why some people develop cirrhosis (around 30% of heavy drinkers), whilst other people develop different complications. Withdrawal symptoms are common.

Consider function

Well-being relates to both severity of disease and the underlying cause. Heavy drinking has profound social effects.

Box 1.35 **Complications of alcohol misuse**

- Chronic liver disease and cirrhosis
- Peptic ulcer disease
- Chronic pancreatitis
- Cerebellar disease (acute dysfunction, chronic degeneration)
- Peripheral neuropathy
- Myopathy
- Wernicke's encephalopathy / Korsakoff's psychosis / dementia
- Hypertension
- Cardiomyopathy
- Malignancy (more common in heavy drinkers, with increased risk of oral, pharyngeal, laryngeal, oesophageal, liver and breast cancer)

Box 1.36 **Abnormal blood tests with alcohol misuse**

- Raised γ-glutamyl transferase, owing to enzyme induction
- Raised aspartate aminotransferase and transaminases (and raised bilirubin, raised alkaline phosphatase and low albumin)
- Raised mean corpuscular volume, owing to alteration in the red blood cell membrane lipid profile
- Thrombocytopenia (haematinic deficiency, hypersplenism, marrow toxicity)
- Low urea owing to nutritional deficiency
- Raised white cell count

Discussion

How would you classify alcoholic liver disease (ALD)?

ALD ranges from steatosis to alcoholic steatohepatitis and established cirrhosis. Fatty change can be seen within days of ingestion on ultrasound, hepatitis ensues with continued exposure with a swollen, smooth and tender liver, with ultimate progression to typically micronodular cirrhosis.

What is alcoholic hepatitis?

Alcoholic hepatitis is a clinical syndrome of jaundice, abdominal pain, fever and leucocytosis after sustained alcohol consumption, and appears to be much more common these days, with increasing hospital admission rates.

Pathophysiology

Alcohol is metabolised by alcohol dehydrogenase to acetaldehyde and by CYP2E1 / Fe. Several mechanisms are involved in the pathophysiology of ALD, and include immunological damage (cytokines mediate damage in the inflammatory response to the breakdown products of alcohol metabolism) with necrotic inflammation or apoptosis, oxidative damage secondary to alcohol metabolism with lipid peroxidation, endotoxaemia leading to tumour necrosis factor-α-mediated cell damage and death, and the formation on cell membranes of protein adducts that initiate an inflammatory response. Although a clear dose–response relationship exists between the risk of ALD and alcohol consumed, additional risk factors include genetic predisposition and polymorphism, patterns of alcohol ingestion, gender, nutritional status, obesity, and coexisting liver diseases such as hepatitis C.

Diagnosis

Diagnosis requires a combination of history, clinical and laboratory results (Box 1.36) and the exclusion of other liver diseases. Liver biopsy may be necessary in atypical cases. Presentation varies from incidental blood test abnormalities through to overt liver failure.

Treatment and prognosis

The key to management is long-term abstinence and care should be delivered in conjunction with addiction services. Protein-calorie malnutrition is common, and addressed along with specific thiamine replacement. Acute severe alcoholic hepatitis has a high mortality, and prognostic scores, such as the discriminant function and Glasgow alcoholic hepatitis score, have been derived to identify those at highest risk and those who may benefit from corticosteroids or pentoxifylline. Scoring takes account of five factors – age, white cell count, urea concentration, prothrombin time and biliribin level – to produce a score out of 15, survival being good with ≥ 9 and poor < 9. Sustained bilirubin levels after 1 week may suggest non-response and poor outcome and the risk of corticosteroid side effects becomes unwarranted. Cirrhotic patients require hepatoma screening and variceal screening endoscopy. Liver transplant should be considered if the clinical condition does not improve despite a period of abstinence.

What is alcohol withdrawal syndrome?

This occurs early, with an onset within 2 hours, a peak at 24–48 hours and duration of up to a week. It comprises tremor, sweating, anorexia, nausea, anxiety, insomnia, tachycardia and hypertension. Withdrawal seizures tend to occur in the first 4 days, peaking at 12–24 hours, and are more likely in those with deranged electrolytes or brain damage. Delirium tremens usually occurs at 48–72 hours, with confusion, agitation, hallucinations and paranoia. It has a mortality of 5–10%, especially in older people, often with arrhythmias.

What is detoxification and how is it implemented?

Detoxification aims to relieve symptoms and prevent complications (seizures and delirium tremens). Benzodiazepines / chlordiazepoxide is used. Detoxification does not remove addiction and is but the first stage of alcohol abstinence. Ideally detoxification could occur at home with trained community nurse support.

What do you know about Wernicke's encephalopathy?

Wernicke's encephalopathy refers to the abrupt onset of confusion and decreased consciousness with ataxia and ophthalmoplegia. Its pathology lies in the brainstem around the third and fourth ventricles. Without intervention, 20% of people die, 70% progress to Korsakoff's psychosis and only 10% recover. Treatment of suspected or established Wernicke's encephalopathy comprises two paired vials of vitamins B and C (Pabrinex) intravenously for 3 days, then one paired vial daily for a further 3–5 days; immediate intravenous normal saline or dextrose 100 ml over 30 minutes is also needed. In high-risk groups, a pair of vials should be given immediately followed by once daily for 3–5 days. In low-risk groups, thiamine 200 mg q.d.s. is important.

What do you know about non-alcoholic steatohepatitis and non-alcoholic fatty liver disease (NAFLD)?

NAFLD is the hepatic manifestation of the metabolic syndrome (central obesity, insulin resistance, hypertension, abnormal glucose tolerance and dyslipidaemia), sometimes termed obesity-induced liver disease. NAFLD is now the leading cause of liver dysfunction in the Western world, with a prevalence of around 30% in the UK, predicted to rise to 50% by 2050. It occurs in patients who have not consumed excessive quantities of alcohol, but it may coexist with and worsen liver damage from any other cause. As well as the metabolic syndrome, rapid weight loss, starvation and some drugs (such as tamoxifen and corticosteroids) can cause NAFLD.

NAFLD defines the spectrum from simple fatty liver or hepatosteatosis to non-alcoholic steatohepatitis to steatohepatitis with fibrosis to cirrhosis, liver decompensation, and hepatocellular carcinoma. Its pathogenesis involves insulin resistance, predisposing to hepatic fat deposition, consequent increased oxidant stress, activation of matrix-producing cells and propagation of fibrogenesis with increasing indication for liver transplantation. There is emerging evidence that maternal obesity may programme offspring obesity with susceptibility to NAFLD via permanent changes *in utero* and lactation.

Fatigue and abdominal pain are sometimes reported but are uncommon. Most patients are asymptomatic and NAFLD is discovered incidentally on liver tests or hepatic ultrasound.

No biochemical threshold has been specified for diagnosing NAFLD, but persistent elevation of alanine aminotransferase or γ-glutamyl transferase, for example, warrants further assessment. Raised alkaline phosphatase levels may occur. Bilirubin levels are usually normal. Ferritin levels are often raised. NAFLD is likely if there are typical risk factors for the metabolic syndrome together with persistent elevation of alanine aminotransferase or γ-glutamyl transferase, an ultrasound consistent with hepatic steatosis and other common or treatable causes of abnormal liver tests have been excluded (e.g. alcohol, viral hepatitis, haemochromatosis). However, normal liver function tests are not always reassuring. Non-invasive imaging remains poor at determining disease extent and there is no clear guidance as to when to biopsy. Proponents of biopsy would argue that 10% of patients with abnormal liver function tests and a negative 'liver screen' who are assumed to have NAFLD have an alternative diagnosis, that liver function tests do not predict fibrosis and cirrhosis and that diagnosing cirrhosis identifies the need for screening for complications such as hepatocellular carcinoma; opponents argue that there is significant error in biopsy specimens, biopsy carries risk and there are few data to support it changing outcome.

Weight loss is fundamentally important. Treatment with metformin, glitazones, vitamin E, angiotensin receptor blockers, α-adrenoceptor antagonists and gastric banding await more robust evidence.

Prognosis depends on disease stage. Patients with simple steatosis have a relatively benign course, with cirrhosis developing in 1–2% over 15–20 years. However, NAFLD is a marker of cardiovascular risk that should be addressed.

Is alcohol protective?

This has been debated for years. It probably is moderately protective in moderation against atherosclerosis, but increases the risk of hypertension. Any protection is probably not exclusive to red wine, a popular notion.

Is drinking a socioeconomic disease?

Drinking patterns in the UK tend towards binges and drinking outside mealtimes. Drinking is a problem of socioeconomic class, with those in low socioeconomic groups tending to not drink at all or drink exceptionally heavily; this, together with a tendency to poor eating habits and the 'double-hit' insults of alcohol and NAFLD, may be lethal factors.

CASE 1.30 VIRAL HEPATITIS

Instruction

This 45-year-old man has a history of intravenous drug misuse. Please examine his abdominal system and discuss your findings.

Recognition

General *signs of chronic liver disease* may be present (Case 1.26).

Interpretation

Confirm the diagnosis

Tell the examiners you would explore risk factors for chronic viral hepatitis. Remember that two or more causes of CLD may coexist.

What to do next – consider causes

Tell the examiners that the history might also suggest other causes of CLD (Case 1.26).

Consider severity / decompensation / complications

Most viral hepatitis morbidity and mortality result from cirrhosis and hepatocellular carcinoma (HCC). Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26).

Consider function

Well-being relates to both severity of disease and the underlying cause.

Discussion

What are the phases of hepatitis B virus (HBV) infection?

The virus

HBV has a massive worldwide prevalence, largely because its genome is incorporated into infected host cells even where it is contained and not detectable in blood. The HBV virion comprises a surface envelope bearing the surface antigen (sAg) and a core containing the core antigen (cAg). A further antigen, eAg, arises from the same gene (C gene) as cAg. The C gene has two initiation codons: a pre-core and a core region. When translation is initiated at the pre-core region, the protein product is HBeAg, which has a signal peptide that facilitates its secretion into the serum. When translation is initiated at the core region, the protein product is HBcAg, which lacks a signal peptide, is not secreted and is not detectable in serum; in this situation there is eAg negativity but there may be significant disease activity.

The natural history

The clinical spectrum varies from an asymptomatic carrier state to fulminant hepatic failure. An intact immune system is vital to HBV clearance; the more vigorous the response (and florid the clinical picture), the greater is the chance of clearance. Most offspring of affected mothers progress to chronic carriage, whereas only a small minority of adults are chronic carriers. HBV infection has four phases (Table 1.35). Factors influencing the natural history through the four phases include host (age, immune status, concurrent infection with other virus and alcohol) and viral (HBV genotype and genome mutants) factors.

What is meant by HBV chronic carriage and what are the markers of high and low infectivity in carriers?

Chronic carriers may still be in phase 2 disease pre-seroconversion and generally of higher infectivity, or in phase 3 disease post-seroconversion and generally of lower infectivity. HBV DNA detectability is the best test of ongoing infectivity. The markers are summarised in Table 1.36.

What are the markers of past HBV infection?

Anti-HBs must be positive before complete recovery from HBV infection and immunity can be inferred. Anti-HBe and anti-HBc immunoglobulin G (IgG) positivity persists. All other markers are negative.

What is HBV pre-core mutant disease?

A variant C gene fails to produce HBeAg capable of secretion into the serum but otherwise causes typical viral-replicating disease. The negative HBeAg test is a misleading false negative and HBV DNA is necessary to detect the presence of disease activity (normal liver enzymes may also mislead and can be associated with significant disease activity). Pre-core mutant strains are common and may develop late in the disease process and lead to reactivation of disease – increasing viraemia and hepatitis even in stage 4 in the absence of HBe antigenaemia reflects the emergence of a pre-core mutant stain.

What do you know about treatment of acute HBV infection?

Most episodes of symptomatic HBV infection resolve without the need for treatment. However, acute HBV infection is associated with high serum HBV DNA, reflecting high viral replication and the potential for infection of non-infected cells and antiviral nucleoside or nucleotide analogues may have a role in early treatment in some patients – those with severe acute hepatitis with a prolonged international normalised ratio, a protracted course with high transaminases or those at increased risk of chronicity, such as immunosuppressed patients.

Why is treatment of chronic HBV infection important?

HBV infection is a global health problem. Around 400 million people are chronically infected with HBV, and in the UK the prevalence is increasing, largely through migration. Most patients acquire infection in early life, often as newborns. HBV infection may be associated with serious extrahepatic manifestations such as vasculitis or nephritis, but most morbidity and mortality are the result of progression to cirrhosis and HCC.

Table 1.35 Phases of hepatitis B virus (HBV) infection (in patients infected with HBe-positive virus)

	Phase 1 **Incubation / active viral replication**	**Phase 2** **Continued replication of virus and inflammatory response**		**Phase 3** **Post-seroconversion**	**Phase 4** **Clearance**
Clinical features	Usually asymptomatic Lasts a few weeks	Widely varied time course – from a few weeks to many years		Begins once immune response eliminates or greatly diminishes infected cell load. Essentially infection is cleared but HBsAg remains positive because sAg gene has been inserted into the host's genome	Resolved or cured
		Acute disease Asymptomatic (70%) or symptomatic (30%) acute hepatitis illness; very rarely fulminant hepatitis	Chronic disease Around 5–10% of adults progress to chronic carriage, which may persist for years (400 million chronic carriers worldwide!)		
HBsA	Positive	Positive		Positive	Negative (most eventually reach this stage)
Anti-HBs	Negative	Negative		Negative	Positive (also positive after HBV vaccination)
HBeAg	Positive	Positive Still secreted by infected liver cells	Seroconversion refers to loss of HBeAg, usually with the appearance of anti-HBe May be early after acute hepatitis In chronic HBV infection the spontaneous seroconversion rate is only a small percentage per year	Negative	Negative
Anti-HBe	Negative	Negative		Positive	Positivity persists lifelong (negative in HBV-vaccinated individuals who are only anti-HBs positive)
Anti-HBc	IgM positive IgG negative	IgM negative / low titre IgG high titre		IgM negative IgG moderate titre	IgM negative IgG positivity persists lifelong (negative in HBV-vaccinated individuals who are only anti-HBs positive)
Serum HBV DNA	Positive (indicating active viral replication)	Positive but significant decline with seroconversion		May still be detectable in some by PCR	Undetectable by PCR (implies reactivation or reinfection unlikely)
Transaminases	Normal	Raised		Normal	Normal
Histology	Chronic persistent hepatitis	Chronic active hepatitis Cirrhosis more likely if seroconversion is delayed		Inactive or minimal hepatitis or inactive cirrhosis	No significant disease, especially if seroconverted before cirrhosis Chronic active hepatitis if reactivation or emergence of HBV variant Hepatocellular carcinoma

Ig, immunoglobulin; PCR, polymerase chain reaction.

Table 1.36 Indications for treatment of hepatitis B virus infection

	Hepatitis	**Cirrhosis**
	HBeAg positive or negative	Compensated or decompensated
Alanine aminotransferase	> upper limit of normal	Any value
Viral load	> 2000 IU / ml	Detectable
Biopsy	Moderate / severe inflammation and/or fibrosis	

Which patients with chronic HBV infection should be treated?

The main goal of treatment is to prevent cirrhosis. The timing and choice of antiviral therapy depend on the patient profile. Antiviral treatment can alter the natural history, as suppression of HBV replication delays or prevents fibrosis and cirrhosis, enables recovery from decompensation and reduces the risk of HCC. Most patients with chronic HBV infection do not develop clinically significant liver disease, and have low levels of viral replication with HBeAg negativity and low levels of HBV DNA ($< 10^4$ IU/ml). These patients were formerly termed 'healthy carriers' but serum titres can subsequently rise causing inflammation and fibrosis, necessitating lifelong surveillance. There is a clear correlation between serum HBV titres and the risk of liver damage; low titres ($< 10^4$ IU/ml) are unlikely to be associated with progressive liver damage, but high titres appear to be a prerequisite for liver damage (although a few young HBeAg-positive patients with high titres have little inflammation and are said to be in an immunotolerant phase). Thus, high serum HBV titres or viral loads are an essential but insufficient indication for antiviral treatment, and likely candidates also have biochemical or histological evidence of inflammatory disease. Indications for treatment in HBV infection are outlined in Table 1.36. High serum HBV titres may be associated with HBeAg positivity or negativity and HBeAg-negative hepatitis is not uncommon, especially in older patients who may have advanced fibrosis or cirrhosis and who will inevitably have experienced a period of HBeAg-positive hepatitis in the past. Significant liver disease and need for transplantation is more likely in males.

How is chronic HBV infection treated?

Two classes of drug are licensed and approved for the treatment of HBV, as follows.

Pegylated interferon-α (PEG-IFN)

Polyethylene glycol added to IFN as PEG-IFN allows it to be injected weekly. PEG-IFN upregulates the immune response to the virus. Favourable response to IFN is more likely with HBV genotype A or B, lower viral load, alanine aminotransferase levels more than twice the upper limit of normal, female gender, age less than 50 years and acquisition of infection in adulthood. IFN has the advantage of a defined treatment duration, usually 6–12 months. Sustained viral suppression with normalisation of liver function tests is achieved after 1 year in approximately 30% of HBeAg-positive and 15% of HBeAg-negative patients.

Nucleotide/nucleoside analogues

These include lamivudine, adefovir, tenofovir and entecavir. They are generally well tolerated and require minimal monitoring, but optimal treatment duration is unclear. They may be preferred in cirrhosis, HBV/human immunodeficiency virus (HIV) co-infection and immunosuppressed patients. A trial of drug withdrawal may be attempted in HBeAg-positive patients who become HBeAg-negative on treatment, but for most patients treatment should be considered long term. Rates of drug resistance are high with lamivudine (up to 70% at 5 years). For this reason it is recommended to initiate treatment with newer agents with potent rapid antiviral activity and low risk of resistance (entecavir and tenofovir). There is crossover in viral resistance mutations, so sequential use of antiviral agents is not encouraged and the management of escape mutants should be with addition of appropriate second-line agents.

Overall cure rates are not as encouraging as once hoped, because the viral genome can persist in hepatocytes despite sustained and potent suppression. There is no apparent benefit of combining IFN with a nucleotide/nucleoside analogue. For selected patients with decompensated cirrhosis, liver transplantation may be appropriate.

What are the key methods of prevention of chronic HBV infection?

All of this highlights the importance of prevention through education, immunisation programmes (which may ultimately become universal in the UK) and screening of newborn babies.

What do you know about the epidemiology of the hepatitis C virus (HCV)?

HCV infection is a major public-health concern, globally much more prevalent than HIV infection. Over 180 million people worldwide have chronic HCV infection and are at risk of its life-threatening complications. The UK prevalence is unknown but estimated at around 0.5%. Acute infection is usually clinically silent (transaminases would be elevated) but occasionally produces jaundice, and whilst some clear the virus spontaneously it is associated with a high chronic carrier state (80%), progression to cirrhosis in many chronic carriers and a 1–4% annual risk of HCC in those with cirrhosis.

How is HCV transmitted?

HCV is a single-stranded RNA virus of six genotypes (and many subtypes) with differences in pathogenicity, treatment response and prognosis. The two most important routes of transmission are sharing of needles or equipment by injecting drug users and transfusion of blood and blood products (now virtually eliminated in the UK since screening of donors in 1991). Potential routes include sharing of toothbrushes and razors, tattooing, body piercing, electrolysis and acupuncture. Sexual transmission and maternal vertical transmission rates appear to be low. Occupational risk in health-care workers is significant because HCV may be transmitted in many body fluids. The risk of transmission from an HCV needlestick injury is about 1:30.

How is HCV diagnosed?

The HCV antibody test is positive at 6 months after exposure but the RNA virus can be detected by polymerase chain reaction.

How is HCV disease severity assessed?

Liver biopsy is the only satisfactory way to assess severity, because serum transaminases may fluctuate disproportionately with activity.

Which patients with chronic HCV infection should be treated?

Current recommendations are to offer combination therapy to all patients with chronic HCV infection who do not have contraindications to treatment. Those with mild disease and unfavourable genotypes or a predicted poor chance of treatment response may choose to defer treatment until newer agents are available. Treatment may not be needed, and IFN has a higher incidence of side effects than for HBV infection. A substantial proportion of patients with acute symptomatic HCV infection clear the virus without treatment, and delaying treatment for a few months seems not to compromise the very high rates of clearance produced at that stage with treatment.

How is chronic HCV infection treated?

The aim of current treatment regimens for chronic HCV infection is sustained virological response, defined as undetectable serum HCV RNA 6 months after the end of therapy. Clearing HCV prevents progression of fibrosis, reducing the risk of hepatic decompensation and HCC. The standard treatment is combination therapy with PEG-IFN and ribavirin – a single course of treatment for 48 weeks for genotype 1 or 4 and 24 weeks for genotype 2 or 3 HCV, with respective sustained virological response (cure) rates of approximately 45% and 80%. Treatment at all stages of HCV infection, including mild fibrosis, is cost effective. Treatment in decompensated cirrhosis should be undertaken only in specialist centres with access to transplantation. Duration of treatment may be shortened for selected patients with an undetectable viral load after 4 weeks of treatment (rapid virological response), which appears to be a marker of likelihood of successful eradication. Response may be improved with 72 weeks of therapy in patients with genotype 1 infection who have a slow initial response. Response rates are lower for those with a higher baseline viral load, more advanced liver disease, higher body mass index, ongoing excessive alcohol use, non-Caucasians, co-infection with HIV and patients not taking full treatment courses. IFN is associated with side effects in approximately 75% of patients, most commonly flu-type symptoms such as myalgia, arthralgia, fatigue, headache and fever. It is also associated with myelosuppression, autoimmune conditions and neuropsychiatric illness. The major side effect of ribavirin is haemolytic anaemia. Ribavirin is potentially teratogenic. Viral protease inhibitors (e.g. telaprevir, bocepravir), combined with the above as triple therapy, appear promising.

List some other causes of acute infective hepatitis

These include hepatitis A and E viruses, Epstein–Barr virus, cytomegalovirus and herpes simplex virus hepatitis, parvovirus and atypical pneumonia organisms. In certain groups such as pregnant women and immunocompromised patients, these viruses can, rarely, cause fulminant hepatic failure. While some antiviral therapies can be used, the majority of cases are managed expectantly. At-risk populations (travellers and the immunocompromised) should be offered vaccination where available.

CASE 1.31 AUTOIMMUNE HEPATITIS

Instruction

Please examine this 45-year-old woman's abdominal system and comment on possible diagnoses.

Recognition

General *signs of chronic liver disease* (CLD) (Case 1.26) may be present, e.g. spider naevi (Fig. 1.52).

Interpretation

Confirm the diagnosis

Criteria proposed by the International Autoimmune Hepatitis Group exist for diagnosing autoimmune hepatitis (AIH; Box 1.37) although you cannot determine this from clinical examination. Even where criteria are fulfilled, additional causes of CLD should be excluded.

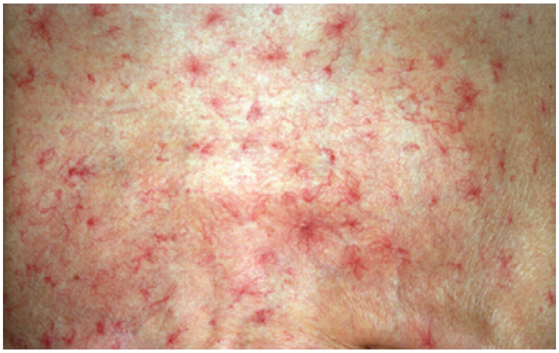


Figure 1.52 Spider naevi, common in type 1 autoimmune hepatitis.

Box 1.37 **Criteria for the diagnosis of autoimmune hepatitis**

Major

- Hypergammaglobulinaemia (preferentially immunoglobulin G) on serum electrophoresis with immunoglobulin subtypes
- Autoantibodies (antinuclear antibody and antibodies to: smooth muscle antigen, soluble liver antigen, liver–kidney–microsomal antigen)
- Absence of viral hepatitis
- Portal hepatitis (with lymphoplasmacellular infiltrates) on biopsy

Minor (give further support to diagnosis but not essential)

- Personal or family history of autoimmune disease
- Spontaneously fluctuating course
- Arthralgia
- Presence of HLA-DR3 or DR4

What to do next – consider causes / assess other systems

Causes

Consider the causes of CLD (Case 1.26). Tell the examiners that you would ask about alcohol consumption, previous jaundice, previous transfusions, drug use, occupation, travel and sexual history. Look for signs of other autoimmune diseases, especially thyroid disease (face) and rheumatoid arthritis (hands).

Symptoms

Tell the examiners that you would ask about symptoms. AIH is a relatively uncommon diagnosis that often affects young women. The usual presentation is non-specific, with fatigue, slight right upper quadrant pain, polymyalgia / arthralgia and abnormal liver function tests. The female–male ratio is 3 : 1. Other autoimmune conditions are present in up to 60% of patients – notably keratoconjunctivitis sicca, renal tubular acidosis, peripheral neuropathy, Hashimoto's thyroiditis, ulcerative colitis and rheumatoid arthritis. AIH can produce transient jaundice or may be detected serendipitously as an isolated transaminase rise. It may remain subclinical and undetected until cirrhosis provokes hepatic decompensation.

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26). AIH may progress rapidly to cirrhosis.

Consider function

Well-being relates to both severity of disease and side effects of treatment.

Discussion

What types of autoimmune hepatitis (AIH) do you know of?

AIH is a progressive necro-inflammatory liver disease associated with significant morbidity and mortality. It affects mainly females and clinical presentation varies from minor symptomatology to acute liver failure. The diagnosis should be considered in anyone with abnormal liver function tests. Diagnostic features include biochemical evidence of transaminitis, elevated immunoglobulin G and positive autoantibodies. Liver biopsy may show interface hepatitis with portal-based plasma cell infiltrates. Types of AIH are described in Table 1.37.

How important is treatment for AIH?

Treatment of AIH switches a dismal prognosis to an excellent one with a normal life expectancy in the vast majority. The difficulty is that presentation is often delayed because of subclinical disease.

What is the treatment for AIH?

Immunosuppression with corticosteroids produces prompt induction of remission (prednisolone 1 mg / kg initially or budesonide). Azathioprine is the drug of choice for maintenance of remission (50–100 mg daily). Regimens vary. Treatment is continued for at least 3 years but often lifelong as relapse is common if treatment is stopped. Mycophenylate mofetil may be used for patients intolerant of azathioprine (myelosuppression, hepatotoxicity, pancreatitis). Late-diagnosed AIH is an indication for considering transplantation.

What is the AIH overlap syndrome?

Between 10% and 20% of patients have overlap with primary biliary cirrhosis or primary sclerosing cholangitis.

CASE 1.32 PRIMARY BILIARY CIRRHOSIS

Instruction

Please examine this woman's skin and abdomen. Discuss your findings.

Recognition

General *signs of chronic liver disease* (CLD) (Case 1.26) may be present.

Table 1.37 Types of autoimmune hepatitis (AIH)

	Type 1	Type 2	Type 3
Epidemiology	Classic type Around 80% of AIH	Around 10% of AIH, more prevalent in children	Small subgroup
Clinical features	Chronic or acute Palmar erythema and spider naevi common		Similar to type 1
Autoantibodies	Both ANA and SMA (directed at actin) antibodies present in 40–50% SLA / LP antibodies in 20% – in half of these the only demonstrable antibody (ANA / SMA / LKM antibodies may be found in other diseases; SLA / LP antibodies highly specific for AIH but missed on routine immunofluorescence)	LKM antibodies directed at cytochrome P450IID6	SLA antibodies directed at UGA-suppressor and tRNA-associated protein
Other tests	Polyclonal (especially IgG) hypergammaglobulinaemia	Type 2b associated with LKM antibodies and HCV infection	ANA / SMA / LKM antibodies not present No significant hypergammaglobulinaemia
Treatment	Corticosteroids	Corticosteroids (rapidly progressive without treatment)	Corticosteroids (rapidly progressive without treatment)

ANA, antinuclear antibody; HCV, hepatitis C virus; IgG, immunoglobulin G; LKM, liver–kidney–microsomal antigen; SLA / LP, soluble liver antigen; SMA, smooth muscle antigen; UGA, uracil–guanine–adenine.

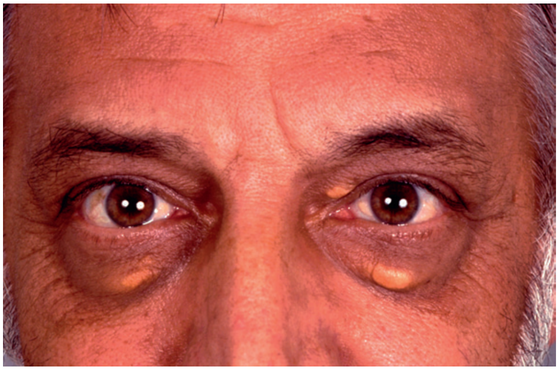


Figure 1.53 Xanthelasmata.

Interpretation

Confirm the diagnosis

Consider the causes of CLD (Case 1.26). Tell the examiners that you would ask about alcohol consumption, previous jaundice, previous transfusions, drug use, occupation, travel and sexual history. In primary biliary cirrhosis (PBC) there may be prominent scratch marks (due to itch). Xanthelasmata (Fig. 1.53) affect 5–10% of patients.

What to do next – assess other systems

Tell the examiners that you would ask about symptoms:

- Fatigue and pruritus (20–70%) are the most common presenting symptoms, preceding jaundice by months to years.
- Right upper quadrant discomfort affects a small number of patients. PBC may first present as variceal bleeding, illustrating the importance of pre-emptive investigation of patients with isolated alkaline phosphatase elevation, but portal hypertension, variceal bleeding, ascites or hepatic encephalopathy are usually late features.

Other common findings in PBC are osteopenia, hyperlipidaemia and coexisting autoimmune diseases, notably thyroid disease, Sjögren's / sicca syndrome, Raynaud's / scleroderma, rheumatoid arthritis and coeliac disease. Less common are interstitial lung disease, sarcoidosis, renal tubular acidosis and autoimmune blood disorders.

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26). In addition to hepatic decompensation, steatorrhoea and malabsorption may lead to osteomalacia with bone pain, but this tends to be late in the course of disease.

Consider function

Well-being relates to both severity of disease and side effects of treatment.

Discussion

What causes primary biliary cirrhosis (PBC)?

PBC is a slowly progressive cholestatic autoimmune disease primarily affecting women, with a peak incidence

Box 1.38 Diagnosis of primary biliary cirrhosis (PBC)

- Antimitochondrial antibody (AMA) – M_2 subtype – positivity; antinuclear antibody (ANA) often, but not invariably, positive
- Elevated liver enzymes (> than 6 months)
- Diagnostic histology – liver not affected uniformly but four general stages are portal triad inflammation, bile duct depletion, extending inflammation and cirrhosis

Diagnosis is probable with two of the three features, although AMA positivity to various pyruvate dehydrogenase complex (PDC)-E subtypes (notably PDC)-E2 is highly specific and virtually diagnostic of PBC, as is an ANA to a nuclear pore protein gp210 (although this occurs in only around 15% of patients); some experts suggest that all patients with PBC become AMA positive but others recognise AMA-negative PBC and call it autoimmune cholangitis.

in the fifth decade. The cause is not known, but there is a strong association with anti-mitochondrial antibodies (AMA). Genetic or environmental factors probably trigger these antibodies, which target 2-oxo-acid dehydrogenase complexes participating in oxidative phosphorylation, especially the pyruvate dehydrogenase E2 complex (PDC-E2). T lymphocytes infiltrating the liver are specific for PDC-E2 and intensely populate the portal tracts, with biliary epithelial destruction. PBC is characterised by granulomatous cholangitis, which leads to progressive destruction of the small and middle-sized intrahepatic bile ducts, leading to fibrosis and cirrhosis. The paradox in PBC is that mitochondrial proteins are present in all nucleated cells but disease is specific to the bile ducts, suggesting that PDC-E2 processing during apoptosis in bile duct cells may differ crucially from PDC-E2 processing elsewhere.

What diagnostic tests are there for PBC?

Diagnosis of PBC is outlined in Box 1.38.

What is the treatment for PBC?

Bile acids (ursodeoxycholic acid (UDCA) 10–15 mg/kg/day) may slow progression, more useful in early disease, delaying fibrosis and variceal evolution. Colestyramine is the main treatment for pruritus, although agents such as rifampicin, naltrexone or even plasmapheresis are effective in some. Transplantation is the only effective treatment for end-stage disease but PBC recurs in about 50% at 10 years.

What is primary sclerosing cholangitis (PSC)?

PSC is a chronic, cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The progressive pathology obliterates intrahepatic and extrahepatic bile ducts, ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure. The cause is unknown but it is closely associated with inflammatory bowel disease, particularly ulcerative colitis, which occurs in about 70% of cases. Approximately 5–10% of patients with total ulcerative colitis have coexisting PSC.

Symptoms include fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus and the clinical course is variable. Serum biochemical tests usually indicate cholestasis and diagnosis is established by cholangiography. Perinuclear antineutrophil cytoplasmic antibody positivity is present in many.

Median survival in symptomatic patients from presentation to death or liver transplantation is 12 years; 75% of asymptomatic patients survive 15 years or more. Most die in hepatic failure following deepening cholestatic jaundice. Some die from aggressive cholangiocarcinoma. Others die from complications of colitis or colorectal cancer.

There is no cure. Medical treatment with UDCA may slow progression and is a chemoprotective agent against colonic dysplasia. Liver transplantation is the only treatment in young patients with PSC and advanced liver disease; 5-year survival is 80–90%. The disease recurs in the donor liver in 30% of patients after 5 years.

Secondary sclerosing cholangitis follows numerous insults including bacterial cholangitis and graft versus host disease.

What is autoimmune pancreatitis?

This is an autoimmune disease producing a cholestatic liver pattern of abnormalities. It may look similar to carcinoma of the head of the pancreas on imaging. It is associated with immunoglobulin G4 levels. It responds well to steroids.

CASE 1.33 GENETIC HAEMOCHROMATOSIS

Instruction

Please examine this 55-year-old man's skin and abdomen and proceed as you think appropriate.

Recognition

There may be *slate greyish pigmentation*. There is *firm, smooth hepatomegaly* +/− splenomegaly. General *signs of chronic liver disease* (CLD) may be present (Case 1.26).

Interpretation

Confirm the diagnosis

Consider the causes of CLD (Case 1.26). The dusky pigmentation in genetic haemochromatosis is characteristic and affects most patients, although some candidates fall into the trap of considering silvery amiodarone skin changes, which affect sun-exposed areas (Fig. 1.54). Generally, the disease presents in middle age, women tending to be diagnosed later than men because of the protection afforded by menstruation. Tell the examiners that a liver

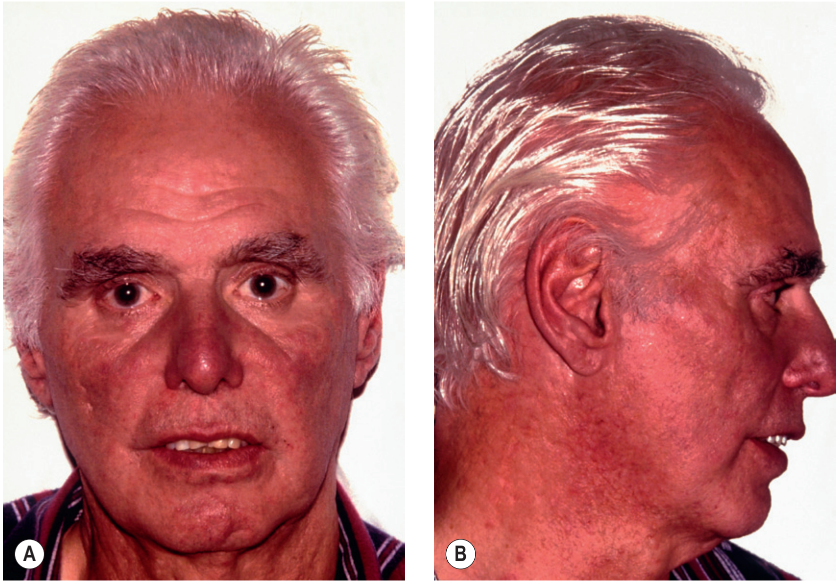


Figure 1.54 Amiodarone skin changes.

biopsy is diagnostic. Secondary iron overload occurs in patients requiring repeated transfusion.

What to do next – assess other systems

The clinical manifestations of genetic haemochromatosis result from iron deposition in major organs, notably the skin, pancreas, heart, liver and anterior pituitary. Tell the examiners you would assess for these (Fig. 1.55).

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26). Hepatocellular carcinoma is the most common cause of death, the relative risk being some 200-fold times that of the normal population. Tell the examiners that ultrasound screening is important.

Consider function

Well-being relates to both severity of disease and to organs involved.

Discussion

What do you know about the genetic basis of genetic haemochromatosis?

It is an autosomal recessive disorder of excessive absorption of dietary iron leading to deposition in several organs and organ failure. The genetic defect responsible for 90% of cases in the UK is homozygosity for a single base mutation (cytosine to tyrosine, C282Y) in the *HFE* gene, closely associated with *HLA A3* on the short arm of chromosome 6p. *HFE* encodes a class 1 human leucocyte antigen (HLA) protein, which, when associated with β_2-microglobulin, is transported to the cell surface where it binds with transferrin receptor-1. The C282Y mutation prevents HFE from associating with β_2-microglobulin but how this leads to iron overload is uncertain. Variable penetrance of the common genotype suggests that other genes modify iron loading and environmental factors such as alcohol are also important for expression of HFE-related haemochromatosis. Less common mutations such as those affecting the transferrin receptor-2 gene and the ferroportin gene underpin less common types of haemochromatosis and interact in a common molecular pathway involving HFE and the regulatory peptide 'hepcidin', which via the iron export protein ferroportin maintains body iron balance.

How is genetic haemochromatosis diagnosed?

Presentation with classical signs relating to end-organ damage is less typical, though joint symptoms are common. Early non-specific symptoms include fatigue, arthralgia, loss of libido, erectile dysfunction, amenorrhoea and increased skin pigmentation. Diabetes mellitus, cardiomyopathy, arrhythmias, cirrhosis and anterior pituitary failure ensue if the condition remains undetected. Clinical manifestations usually become overt by age 40–50. Diagnosis may be suggested by high transferrin saturation (> 55% in > 90%), and confirmed by liver biopsy (excessive iron storage) or genetic testing. Transferrin saturation may be falsely positive in patients taking iron therapy. Serum ferritin may be falsely positive in inflammatory states.

How is genetic haemochromatosis managed?

Early accurate diagnosis is possible and disease entirely preventable through phlebotomy. Liver biopsy is mainly reserved to identify cases for hepatoma surveillance. Penetrance is much lower in females and immediate treatment is not always required in the presymptomatic state. A low clinical index of suspicion avoids delay in diagnosis and family screening is fundamental. Venesection (e.g. 500 ml once or twice weekly until serum ferritin is in the normal range) is effective in removing liver iron, though new oral iron chelators are showing promise.

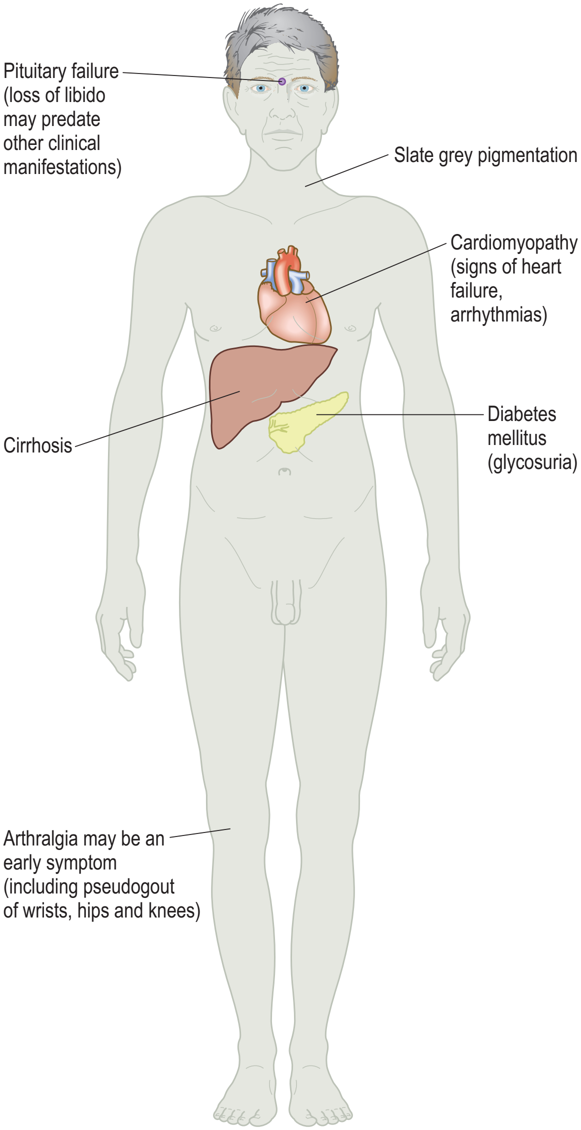

Pituitary failure (loss of libido may predate other clinical manifestations)
Slate grey pigmentation
Cardiomyopathy (signs of heart failure, arrhythmias)
Cirrhosis
Diabetes mellitus (glycosuria)
Arthralgia may be an early symptom (including pseudogout of wrists, hips and knees)

Figure 1.55 Organ involvement in haemochromatosis.

What are the arguments for and against screening?

Patients do not usually develop symptoms until they are over 40 years of age, by which time iron deposition in affected organs may have caused irreversible tissue damage and incipient organ failure. Treatment in early disease can restore normal life expectancy. Although detectable at a presymptomatic stage, and treatable, genetic haemochromatosis does not fulfil all of the criteria for screening. It is relatively uncommon (although many would argue that its homozygous incidence of around 1:300 justifies screening), and the optimal test is contentious. Transferrin saturation only detects expressed disease. Further, the genetic test is not as useful as initially thought. C282Y is not the only mutation, and it is increasingly realised that many people are autosomal recessive for this gene yet are asymptomatic. Thus, the phenotype is not predicted by the genotype. To further complicate matters, asymptomatic autosomal recessive people do seem to be at increased risk if they carry an additional liver insult, notably carriage of the hepatitis C virus.

A suitable compromise is to screen anyone in whom symptoms or signs suggest possible disease, relatives of patients with disease and anyone with unexplained abnormal liver biochemistry (especially those with diabetes).

CASE 1.34 WILSON'S DISEASE

Instruction

Please examine this patient's abdominal system then look briefly at his eyes before discussing your findings.

Recognition

General *signs of chronic liver disease* (CLD) may be present (Case 1.26). Wilson's disease is very uncommon (average population prevalence 30 per million and carrier rate 1:90) but might appear in PACES. The clue from the instruction is to look for *Kayser–Fleischer rings* (Fig. 1.56).

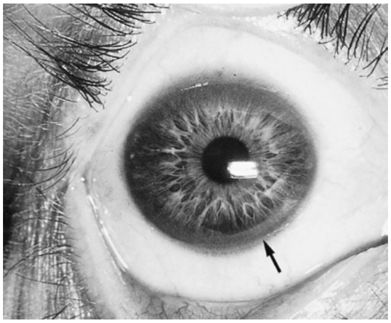


Figure 1.56 Kayser–Fleischer ring.

Box 1.39 **Extrahepatic features of Wilson's disease**

- Kayser–Fleischer rings (much less commonly sunflower cataracts)
- Neurological features due to basal ganglia deposition – tremor, chorea, rigid dystonia, cramped handwriting, poor coordination
- Psychiatric features – depression, neurosis, antisocial behaviour, emotional lability, poor memory, difficulty with abstract thinking
- Fanconi's syndrome due to copper infiltration disrupting renal tubular exchange
- Arthritis
- Cardiac arrhythmias
- Hypoparathyroidism

Interpretation

Confirm the diagnosis

Kayser–Fleischer rings are rusty brown deposits of copper within Desçemet's membrane of the cornea and are pathognomonic of Wilson's disease. They start at 6 and 12 o'clock, are not always present, and sometimes detectable only with a slit-lamp.

What to do next – assess other systems

Extrahepatic features of Wilson's disease are listed in Box 1.39.

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and tell the examiners you would determine the severity of disease (Case 1.26) and that it is important to recognise and treat before neuropsychiatric disease develops.

Consider function

Well-being relates to both severity of disease and side effects of treatment.

Discussion

What is the cause of Wilson's disease?

Wilson's disease is an autosomal recessive disorder of hepatic copper deposition caused by mutations in the *ATP7B* gene on chromosome 13. Different mutations run in different families. This gene encodes a P-type adenosine triphosphatase (ATPase), the Wilson ATPase. This links copper to the copper-carrying protein caeruloplasmin within hepatocytes and releases it into the bloodstream (copper is needed by the body for a number of functions, predominantly as a cofactor), as well as removing excess copper by secreting it into bile. Both ATP7B functions are impaired in Wilson's disease and copper accumulates in the liver tissue without being released into the bloodstream; caeruloplasmin is still secreted, but in a form that lacks copper and is rapidly degraded in the bloodstream.

Box 1.40 **Biochemical abnormalities in Wilson's disease**

- Serum caeruloplasmin low
- Serum copper low
- 24-hour urinary copper excretion high

When is Wilson's disease typically diagnosed?

Diagnosis is typically in children or young adults (5–45 years) but it is under-recognised in older patients.

What hepatic manifestations occur in Wilson's disease?

These include asymptomatic hepatomegaly, hepatitis, CLD and, rarely, fulminant hepatic failure liberating free copper into the bloodstream, whose toxicity destroys red cell membranes and damages renal tubules.

What biochemical abnormalities would you expect in Wilson's disease?

These are shown in Box 1.40.

Clinical investigations include tests of liver function, cerebral imaging, serum caeruloplasmin and copper, basal 24-hour urinary copper measurement, and hepatic parenchymal copper concentration. Genetic diagnosis is complex but definitive, and best used for family studies.

What treatments are available for Wilson's disease?

Treatment is usually effective and consists of lifelong administration of a chelator (D-penicillamine or trientine) or zinc in pharmacological doses. Liver transplantation is nearly always required for patients with fulminant hepatic failure (coagulopathy, encephalopathy, massive intravascular haemolysis, renal failure, elevated aminotransferases, subnormal alkaline phosphatase) or for liver disease unresponsive to medical treatment. Liver cancer is extremely uncommon in patients with Wilson's disease, but screening may be appropriate for older patients.

CASE 1.35 HEPATOMEGALY

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *hepatomegaly* (Fig. 1.57), the liver enlarged to (state in cm) below the costal margin. The spleen is not enlarged.

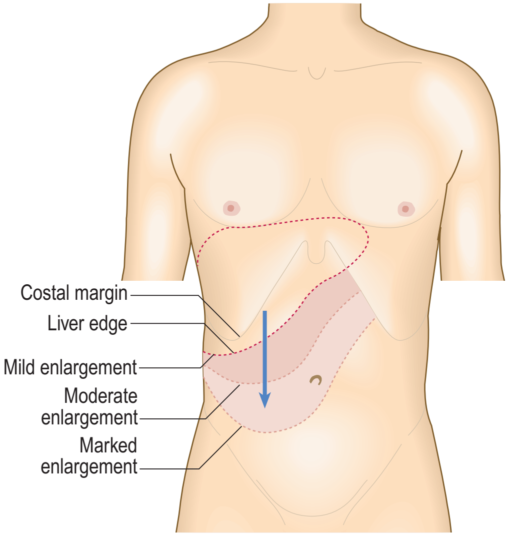


Figure 1.57 Hepatomegaly.

Table 1.38 Signs of common causes of hepatomegaly

Causes (the three 'C's)	Signs
Cirrhosis	Signs of chronic liver disease (Case 1.26)
Cancer (metastatic or primary hepatocellular cancer)	Liver often hard, with nodular edge Cachexia
Cardiac (right-sided heart failure)	Liver firm, with smooth, tender edge; may be pulsatile; liver tenderness suggests recent stretching of capsule due to heart failure or acute hepatitis Raised jugular venous pulse Peripheral oedema

Interpretation

Confirm the diagnosis

Hepatomegaly has numerous causes.

What to do next – consider causes

Look for the signs in Table 1.38.

Other causes include polycystic disease, and infiltrative (e.g. haemochromatosis, AA amyloidosis) and infective causes.

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26).

Consider function

This depends upon the cause.

Discussion

What do know about hepatocellular cancer (HCC)?

Prevalence and risk factors

HCC is one of the commonest malignancies worldwide but with wide geographical variation. It occurs almost always on a background of chronic liver disease (CLD), usually cirrhosis, and is rising in prevalence, in part due to the increasing prevalence of chronic hepatitis C virus (HCV) infection. Other risk factors include chronic hepatitis B virus infection, dietary exposure to aflatoxin, increasing age and male gender. Generally in the West in younger people it is caused by viruses and older people by non-alcoholic fatty liver disease.

Clinical features

Hepatic functional reserve means that tumours can reach considerable size before causing symptoms or signs, typically right upper quadrant pain, hepatomegaly and weight loss. Decompensation of CLD (variceal haemorrhage, ascites, encephalopathy) is also common. HCC may rupture, with severe abdominal pain, shock and haemoperitoneum. Rarely, hypoglycaemia, hypercalcaemia and polycythaemia occur as a result of tumour secretion of insulin-like growth factors, parathyroid-related hormones and erythropoietin, respectively. HCC is increasingly diagnosed in screening programmes.

Investigation

Computed tomography and magnetic resonance imaging show enhancement in the arterial phase with relative hypovascularity ('wash-out') in the portal or late phases; cirrhosis and a mass greater than 2 cm with this radiological appearance, confirmed by two imaging modalities or combined with a serum α-fetoprotein (AFP) greater than 400 ng/ml, is diagnostic of HCC without need for histology. A liver mass not fulfilling these criteria requires histological confirmation. The histological type is not usually of prognostic significance, with the exception of the more favourably prognostic fibrolamellar variant. Cirrhosis independently contributes to prognosis in HCC, as does tumour size; vascular invasion increases with tumour size, but is an independent prognostic factor such that even large tumours can have a good prognosis following surgical resection in the absence of vascular invasion.

Serum AFP is elevated in 70% of patients. Although levels over 500 ng/ml can occur in benign liver diseases, a rising AFP strongly suggests HCC. AFP is also useful in monitoring treatment or detection of recurrence or progression.

Treatment

Surgical resection depends upon tumour size, location, relation to blood vessels and underlying liver function. Fewer than 20% of patients are suitable for resection, although screening may change this. Liver transplantation has the potential to treat both tumour and underlying cirrhosis, although patients with viral hepatitis have a risk of reinfection. Eligibility criteria for liver transplantation are one tumour ≤ 5 cm or up to three nodules, each ≤ 3 cm.

Local ablative therapies may be as effective as surgery in selected cases but, like surgery, are less effective once tumour size exceeds 5 cm; this probably reflects the increasing frequency of vascular invasion and so the likelihood of metastasis. Treatment is usually performed percutaneously under image guidance. Methods include percutaneous ethanol injection and radiofrequency ablation. Transarterial chemoembolisation utilises selective catheterisation of the hepatic artery to deliver regional chemotherapy and embolise tumour-feeding arteries; it is contraindicated in the presence of main portal vein thrombosis, extrahepatic disease, advanced cirrhosis and poor performance status, and may be complicated by abdominal pain, fever and nausea, and occasionally liver abscesses. A major limitation of locoregional approaches is disease recurrence. Most patients with HCC have multifocal disease, bilobar disease, extrahepatic disease and/or underlying cirrhosis. Surgery, ablation or chemoembolisation is not indicated in such patients.

Radiological response rates for single-agent chemotherapy are low (10–15%). The most widely used drug is doxorubicin; combination chemotherapy can induce higher response rates (20–30%), but with no significant impact on survival.

Vascular endothelial growth factor (VEGF) is a key signalling protein stimulated by hypoxia acting predominantly on vascular endothelial cells via VEGF receptor-2 (VEGFR-2). This triggers a tyrosine kinase (TK) signalling cascade that promotes angiogenesis. This process can be inhibited pharmacologically either by a monoclonal antibody targeted against VEGF preventing its interaction with receptor (e.g. bevacizumab) or small-molecule inhibitors of VEGFR signalling (e.g. sorafenib). Sorafenib is an oral multikinase inhibitor whose targets include the raf/mek/erk growth factor signalling pathway. It was the first systemic agent to demonstrate a clear survival advantage in HCC. Sunitinib is another multikinase inhibitor targeting VEGF and platelet-derived growth factor receptor TKs. Many newer agents may not cause tumour shrinkage but rather disease stabilisation.

Antiviral therapy in patients with chronic hepatitis B may reduce the incidence of HCC. There is no vaccine against HCV, but antiviral drugs probably also reduce the incidence of HCC in that situation.

Screening

Those in high-risk groups for HCC should undergo 6-monthly ultrasound screening, serial AFP measurements appearing to be insufficiently sensitive.

List some infective causes of hepatomegaly

- Pyogenic liver abscess
- Amoebic liver abscess
- Hydatid disease

From where might a pyogenic liver abscess arise?

Sources include a subphrenic abscess, biliary sepsis, diverticulitis, appendicitis, Crohn's disease and bacterial endocarditis.

What causes an amoebic abscess?

Entamoeba histolytica is transmitted by the faecal–oral route by ingestion of protozoal cysts. Ten per cent of the world's population is chronically infected. Cyst walls degrade in the small bowel to release trophozoites, which migrate to the large bowel and, assuming a pathogenic strain, cause colitis and invasive disease. Symptoms include right upper quadrant pain and fever.

What is hydatid disease?

This is caused by the dog tapeworm, *Echinococcus granulosus*. The life cycle involves ingestion by the dog of hydatid cysts from sheep liver. The dog, the definitive host, harbours the adult tapeworm in its small bowel, from which eggs are passed into its faeces and reingested by sheep. Humans may be inadvertent intermediate hosts. Eggs hatch in the sheep's small bowel into larvae, which penetrate into the bloodstream, travel to the liver and form cysts.

CASE 1.36 SPLENOMEGALY

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *splenomegaly* (Fig. 1.58), the spleen enlarged to (state in cm) below the left costal margin towards the right iliac fossa. The liver is not enlarged.

Interpretation

Confirm the diagnosis

Splenomegaly has numerous causes.

What to do next – consider causes

These are similar to hepatosplenomegaly (Case 1.37), but an important additional cause is infective endocarditis

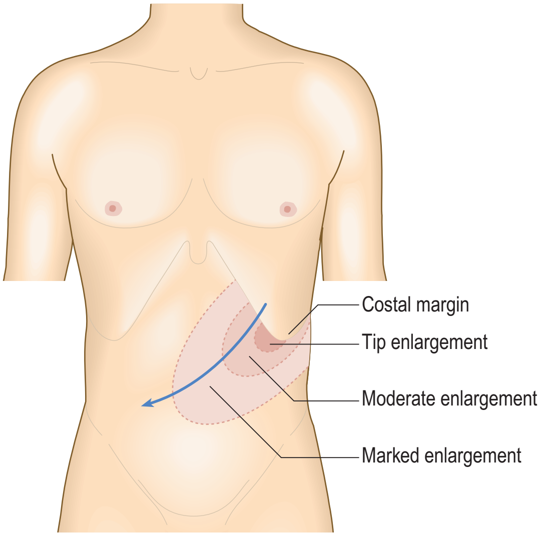


Figure 1.58 Splenomegaly.

(Case 3.11). Look for splinter haemorrhages, Osler's nodes or Janeway lesions. Other causes to consider include portal hypertension, glandular fever, hereditary spherocytosis and Felty's syndrome.

Consider severity / decompensation / complications

Look for petechiae or purpura (hypersplenism).

Consider function

This depends upon the cause.

Discussion

What are the causes of a very large spleen?

These include chronic myeloid leukaemia, myelofibrosis and visceral leishmaniasis, and sometimes malaria.

CASE 1.37 HEPATOSPLENOMEGALY

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *hepatomegaly*, the liver enlarged to (state in cm) below the right costal margin. There is *splenomegaly*, the spleen enlarged to (cm) below the left costal margin towards the right iliac fossa.

Interpretation

Confirm the diagnosis

Hepatosplenomegaly has numerous causes.

What to do next – consider causes

These include:

- Cirrhosis with portal hypertension (congestive splenomegaly)
- Lymphoproliferative disorders (Cases 1.46, 1.47)
- Myeloproliferative disorders (Cases 1.44, 1.45)
- Infection / infiltration.

Consider severity / decompensation / complications

Look for signs of hepatic decompensation (Case 1.26) and for petechiae or purpura (hypersplenism).

Consider function

This depends upon the cause.

Discussion

List some infective and infiltrative disorders of the liver and spleen

- Glandular fever
- Brucellosis
- Leptospirosis
- Sarcoid
- Amyloidosis
- Glycogen storage disorders

CASE 1.38 FELTY'S SYNDROME

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *splenomegaly*, the spleen enlarged to (state in cm) below the left costal margin towards the right iliac fossa. The liver is not enlarged. The patient also has signs *of rheumatoid arthritis* in the hands (Fig. 1.59).

Interpretation

Confirm the diagnosis

Felty's syndrome is the triad of rheumatoid arthritis, splenomegaly and neutropenia.

What to do next – assess other systems

Tell the examiners that you would look for extra-articular signs of rheumatoid disease (Case 5.11). Lympadenopathy may occur.

Consider severity / decompensation / complications

Tell the examiners that you would screen for neutropenia and sepsis.

Consider function

This depends upon the severity of rheumatoid arthritis.

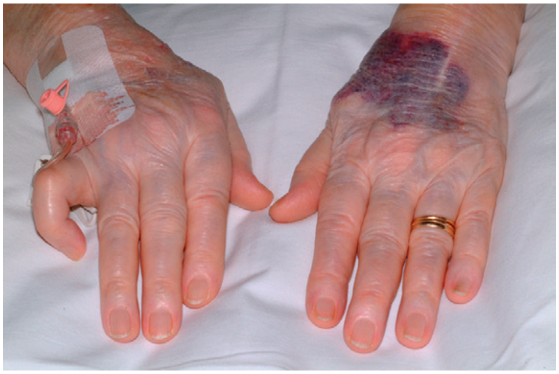


Figure 1.59 Rheumatoid hands.

Discussion

Is rheumatoid factor positive or negative in Felty's syndrome?

Positive.

CASE 1.39 ABDOMINAL MASS

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is an *abdominal mass* – describe it with respect to site, size, shape, surface, edge, consistency (hard or soft), fixation or mobility (with respect to the skin), tenderness and pulsatility.

Interpretation

Confirm the diagnosis

There are many causes. If there is not obvious organomegaly (liver, spleen, kidney), consider the causes in Figure 1.60.

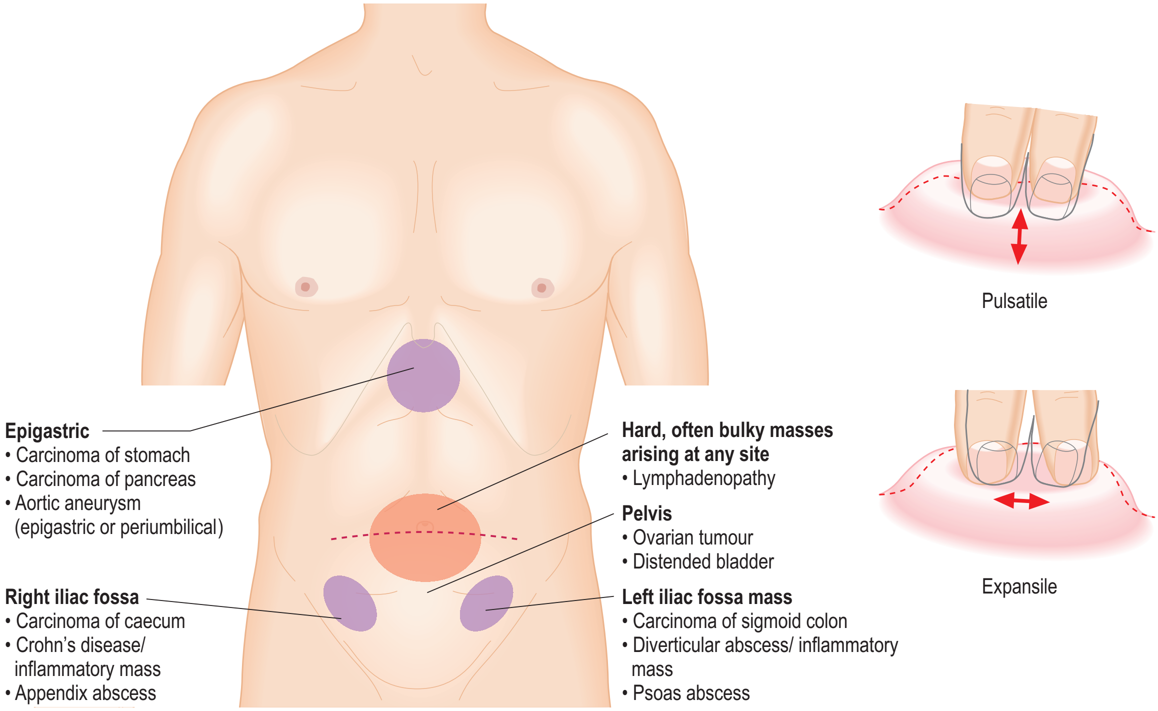

Epigastric
• Carcinoma of stomach
• Carcinoma of pancreas
• Aortic aneurysm
(epigastric or periumbilical)
Right iliac fossa
• Carcinoma of caecum
• Crohn's disease/ inflammatory mass
• Appendix abscess
Hard, often bulky masses arising at any site
• Lymphadenopathy
Pelvis
• Ovarian tumour
• Distended bladder
Left iliac fossa mass
• Carcinoma of sigmoid colon
• Diverticular abscess/ inflammatory mass
• Psoas abscess
Pulsatile
Expansile

Figure 1.60 Abnormal abdominal masses, not enlarged organs.

What to do next – consider causes

Consider the causes in Figure 1.60.

Consider severity / decompensation / complications

Tell the examiners that this relates to cause, e.g. a ruptured aortic aneurysm might become expansile (Fig. 1.60), with abdominal pain and haemodynamic compromise.

Consider function

This depends on the cause.

Discussion

What are the causes of hepatomegaly?

These are discussed in Case 1.35.

What are the causes of splenomegaly?

These are discussed in Case 1.36.

What are the causes of hepatosplenomegaly?

These are discussed in Case 1.37.

List some other causes of an abdominal mass

These are illustrated in Figure 1.60 and Box 1.28 (p. 80).

CASE 1.40 CROHN'S DISEASE

Instruction

Please examine this patient's abdominal system and discuss your findings.

Recognition

There is *perioral aphthous ulceration* (Fig. 1.61). There is a *mass* in the right iliac fossa with evidence of previous surgery from a *midline laparotomy scar*. There may be *erythema nodosum* (Fig. 1.62).

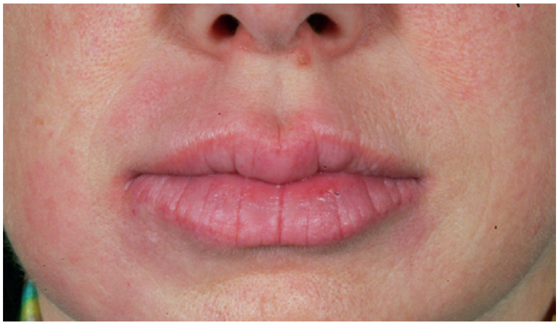


Figure 1.61 Perioral Crohn's disease.

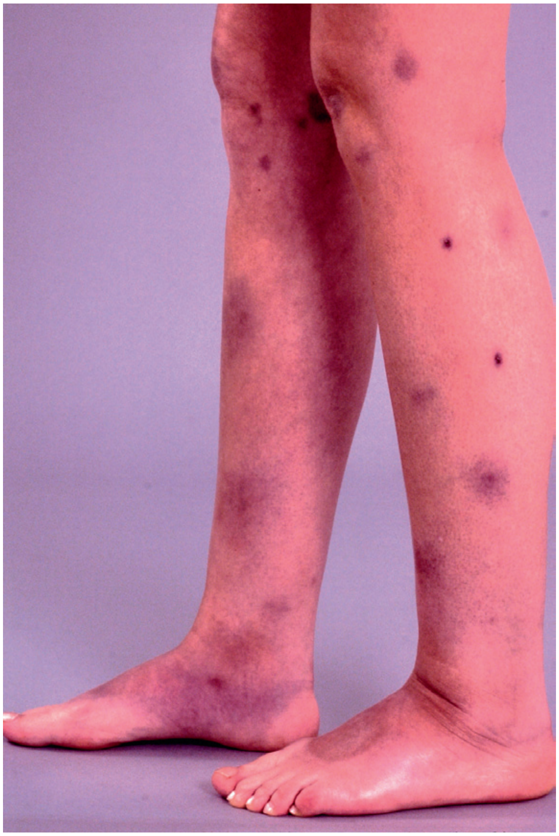


Figure 1.62 Erythema nodosum.

Interpretation

Confirm the diagnosis

Tell the examiners there may be a history of diarrhoea, abdominal pain and bleeding, weight loss and fatigue and that diagnosis is histological.

What to do next – assess other systems

Extraintestinal associations (not usual) can arise in both Crohn's disease (CD) and ulcerative colitis (UC) and may be unrelated or related (most) to disease activity (Table 1.39).

Consider severity / decompensation / complications

Symptoms and complications of the subtypes of CD are outlined in Box 1.41. CD may be classified with respect to affected intestinal site, stenotic or penetrating (fistulising) complications or the degree of active inflammation.

Tell the examiners that colorectal cancer and toxic megacolon are two complications, but that their incidence should be reduced with modern surveillance and treatment.

Table 1.39 Extraintestinal associations of inflammatory bowel disease

Unrelated to disease activity	Joints	Sacroiliitis (18% but usually asymptomatic) Ankylosing spondylitis (rare)
Related to disease activity	Perioral	Aphthous ulceration (20% with CD)
	Skin	Erythema nodosum (5–10%) Pyoderma gangrenosum (more common in UC)
	Joints	Acute arthritis
	Eyes	Uveitis (up to 10%) Episcleritis
	Liver and biliary tract	Gallstones (CD) Primary scleosing cholangitis (UC) Cholangiocarcinoma Fatty change (CD) Amyloidosis (CD) Granulomata (CD)
	Kidneys	Ureteric calculi (oxalate in CD, urate in UC)

CD, Crohn's disease; UC, ulcerative colitis.

Box 1.41 **Clinical subtypes of Crohn's disease (CD)**

Common symptoms including diarrhoea (70–90%), abdominal pain (50%), anal lesions (50–80%), rectal bleeding, fatigue, weight loss and fever are the hallmarks of CD.

Active ileal and ileocaecal disease

Pain is a central feature of ileal and often ileocaecal disease, sometimes with a right iliac fossa inflammatory mass, with or without diarrhoea and weight loss. The pain is constant if caused by inflammation or abscess formation, and colicky with borborygmi and abdominal distension if the result of small bowel obstruction (strictures). Malabsorption may occur.

Active Crohn's colitis

Symptoms are similar to active ulcerative colitis, but frank bleeding is less common. Extraintestinal manifestations are more common with colonic disease.

Perianal CD

There may be fissuring, fistulae or abscesses, and perianal manifestations are more common with colonic disease.

Other

The rectum may be the only site of disease in elderly patients and very rarely CD may be confined to the mouth, stomach or duodenum.

The Montreal classification of CD phenotype refers to age of onset (< 16 years A1, 17–40 years A2, > 40 years A3), location (ileal L1, colonic L2, ileocolonic L3, isolated or with upper gastrointestinal disease L4) and behavior (non-stricturing non-penetrating B1, stricturing B2, penetrating B3, + 'p' if perianal).

Consider function

Tell the examiners that inflammatory bowel disease (IBD) is a chronic, relapsing, often debilitating disease that can have profound psychological as well as physical effects.

Discussion

What do you know about the epidemiology of Crohn's disease (CD)?

Both CD and UC are idiopathic chronic relapsing and remitting disorders. They are increasing in prevalence, more commonly in North America and Europe. CD may present at any age, with peaks at 15–30 years and 60–80 years.

What causes IBD?

The cause is unknown. There is a 10-fold increased relative risk in first-degree relatives. Between 15% and 20% of patients with CD have a relative with CD or UC. Mutations in the *CARD15* (*NOD2*) gene on chromosome 16 have been found in around one-third of patients with CD, especially associated with ileal disease. Environmental associations include non-smoking (UC), smoking (CD), enteric infection (UC), other infections, drugs (including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and oral contraceptives), and high-refined-sugar / low-fibre diets (CD).

What is known about the immunological basis of CD?

Immunological responses (Case 2.46) that colonic bacterial antigens might normally stimulate, including B-lymphocyte-mediated antibody production and T-helper-lymphocyte-mediated production of pro-inflammatory cytokines (tumour necrosis factor-α (TNF-α) is increased in CD, together with nuclear factor-κB (NFκB) and mitogen-activated protein kinases), are normally balanced by downregulatory cytokines, enhanced apoptosis in the lamina propria and absence of co-stimulatory second signals leading to tolerance. It may be that such tolerance mechanisms are deficient in CD. However, as well as this long-held autoimmune theory involving adaptive immunity there is increasing recognition of problems with immunodeficiency in innate immunity and it seems that patients with *NOD2* genetic propensity are less able to clear invasive bacteria whose clearance is dependent on NFκB activation via autophagy gene proteins ATG16L1 and IRGM.

What do you know about the pathology and distribution of CD?

CD is a chronic inflammatory disease with a T-helper-type-1-mediated pro-inflammatory response at its core. It may affect the entire gastrointestinal tract from mouth to anus, especially the terminal ileum (35%), ileocaecal region (40%) and anus/perineum. It is confined to the colon in 20%. The rectum is characteristically spared. There may be skip lesions, with normal mucosa between affected areas. Aphthous ulceration is common, but inflammation tends to be transmural (although predominantly submucosal), often with deep ulceration, fissuring and abscess formation. Histologically, glands are preserved, non-caseating granulomata may occur and the cellular infiltrate tends to comprise lymphocytes, plasma cells and macrophages.

What imaging may be useful in CD?

Ultrasound is sensitive and specific for diagnosing ileal CD. Magnetic resonance imaging has an increasing role.

Should particular drugs be avoided in CD?

NSAIDs and antibiotics may provoke relapse.

Is there a role for dietary advice in managing CD?

High-fat diets appear bad for CD. Elemental diets (containing amino acids and glucose) and polymeric diets may be effective in treating active disease, but are unpalatable. Vitamin supplementation may be necessary in malabsorption.

Are there any non-drug strategies that aid maintenance of remission in CD?

Not smoking reduces the risk of CD and improves maintenance of remission.

What are the treatment objectives in CD?

Treatments are conceptualised in terms of induction and maintenance of remission. Goals are sustained remission with the least toxic therapy and avoidance of complications. At 10 years 75% of patients remain in work.

What are the medical treatments for CD?

Salicylates

5-Aminosalicylic acid (5-ASA) compounds are generally less beneficial for active CD than for active UC. Sulfasalazine 1 g twice daily has traditionally had a role in active colonic disease, but not in maintaining remission, and mesalazine in both active and relapsing CD, but evidence suggests that mesalazine in active CD is little better than placebo and may reduce the risk of relapse after surgery but not after medically induced remission. No maintenance therapy is now recommended in mild disease, other than active non-smoking!

Corticosteroids

Corticosteroids effectively induce remission but do not prevent relapse and are not used long term. CD responds to oral or, if severe, intravenous corticosteroids, regimens similar to those in UC. For mild to moderately active CD, controlled ileal release budesonide at a daily dose of 9 mg is as effective as prednisolone with fewer side effects, and superior to mesalazine or placebo.

Antimicrobials

Antibiotics are appropriate for septic complications, perianal disease in particular. Metronidazole may be helpful in patients with sepsis or bacterial overgrowth, and in Crohn's colitis or fistulating disease. Ciprofloxacin may be helpful in fistulating disease. Attempts to treat CD with antimycobacterial therapy have not shown benefit.

Immunotherapy – immunomodulators and biological therapies

Immunomodulators modify immune function in a generic and less specific way than biological therapies. Biological therapies utilise genetically engineered proteins (e.g. monoclonal antibodies) that target mediators such as cytokines. They are generally administered parenterally, and typically persist in the body for many weeks with long-lasting effects. Both immunomodulators and biological therapies modify disease at the expense of opportunistic infections and other complications.

Immunomodulators such as azathioprine or methotrexate help maintain remission.

In CD, TNF-α mediates inflammation. Infliximab and adalimumab are anti-TNF-α therapies used for induction of response, remission, and maintenance therapy for patients with moderate or severely active CD despite (or because of intolerance to) therapy with corticosteroids and/or immunomodulators. Treatment decisions should be individualised, based on disease activity, previous therapy, disease complications and comorbidity. Relative or absolute contraindications to anti-TNF-α therapy may be memorised by the mnemonic STOIC (sepsis, tuberculosis, optic neuritis, infusion reaction, cancer).

The hope is that earlier use of immunotherapy might alter the pattern of hospital admissions, need for surgery and associated morbidity. Patients with poor prognostic features appear to benefit from early treatment with immunomodulator drugs and/or anti-TNF therapy.

Other therapies

The development of biological therapies continues with other anti-TNF-α agents and those agents outlined in Case 2.46; inhibition of chemokine receptor CCR9, which mediates intestine-specific migration of leucocytes, may prove useful in CD. Other potential therapies include agonists of intestinal growth factor glucagon-like peptide 2, leucocytapharesis and autologous stem cell transplantation. Research is also focusing on the interaction between bacteria and epithelial cells and mediators of mucosal inflammation that may be targets for drug therapies.

What surgical procedures are common for CD?

Right hemicolectomy is the most common operation, but some patients need panproctocolectomy with a permanent ileostomy. Seton insertion for perianal fistulae involves a suture through the fistula track that is tied around the anus to keep the fistula open and prevent abscess formation. As well as enterocutaneous fistulae, fistulae may be enteroenteral, enterovesical or enterovaginal. Improving medical therapy, earlier use of immunosuppressives and anti-TNF agents, and conservative surgical strategies are reducing the need for radical surgical procedures and improving quality of life.

CASE 1.41 ULCERATIVE COLITIS

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is an *ileostomy* in the *right iliac fossa* in this patient with signs of Cushing's syndrome. There may be *pyoderma gangrenosum* (Fig. 1.63).

Interpretation

Confirm the diagnosis

Tell the examiners that there may be a history of diarrhoea, abdominal pain and bleeding and that diagnosis is histological.

What to do next – assess other systems

Extraintestinal associations arise in either Crohn's disease (CD) or ulcerative colitis (UC) or both and may be either unrelated or related (most) to disease activity (see Case 1.40).

Consider severity / decompensation / complications

Bloody diarrhoea is the central feature of UC, although proctitis may present with rectal bleeding and constipation. Truelove and Witt's objective criteria for stratifying UC severity are helpful in defining management (Box 1.42). The natural history may be fulminant, chronic relapsing and remitting, chronic continuous or, occasionally, self-limiting.

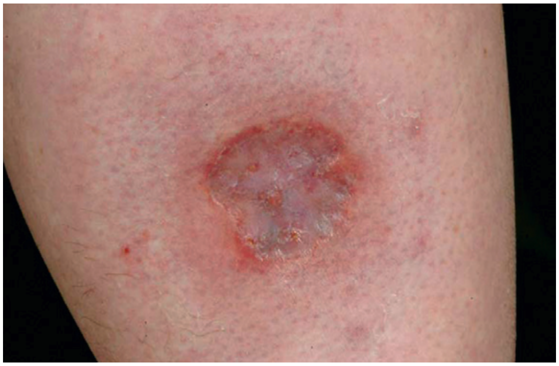


Figure 1.63 Pyoderma gangrenosum.

Consider function

Tell the examiners that inflammatory bowel disease (IBD) is a chronic, relapsing, often debilitating disease that can have profound psychological as well as physical effects.

Discussion

What do you know about the epidemiology of ulcerative colitis (UC)?

Unlike CD, UC shows a bimodal distribution with a major peak between 20 and 40 years and a lesser one between 60 and 80. It presents more commonly in winter.

What causes UC?

The cause is unknown, but in genetically susceptible people, antigens or microbial agents (notably gut microflora) probably trigger an inappropriate dysregulated mucosal immune response. Postulated environmental factors have included sugar, margarine, cornflakes, toothpaste, cola drinks and even household appliances. Only three associations between IBD and environmental agents are clear: a positive association of smoking with CD and the negative associations of smoking and appendicectomy

Box 1.42 Clinical subtypes of ulcerative colitis (UC)

Acute severe UC

Usually total or subtotal colonic disease causing profuse diarrhoea (more than six liquid stools / day), severe rectal bleeding (with mucus), abdominal pain (urgency and cramps before defecation are common, but severe pain should alert you to a complication or another diagnosis) and systemic disturbance (e.g. anorexia, weight loss, fever, tachycardia, anaemia, raised white cell count, raised erythrocyte sedimentation rate).

Moderately active UC

Four to six liquid stools / day, moderate rectal bleeding and some signs of systemic disturbance, or mild disease which fails to respond to treatment.

Mild UC

Less than four liquid stools / day, little or no rectal bleeding and no systemic disturbance.

Proctitis

Rectal bleeding, mucus discharge, tenesmus, urgency, constipation and sometimes pruritus ani.

The Montreal classification of UC phenotype distinguishes extent of inflammation as proctitis (E1), left-sided disease extending up to splenic flexure (E2) and more extensive disease (E3).

with UC. Nicotine has shown some efficacy in inducing remission in UC, although benefit is limited by its side effects. There is a well-established and striking inverse association between UC and appendicectomy. It would therefore seem reasonable to suggest appendicectomy as a treatment option in severe UC or a preventive measure in those at high risk, but this would only apply were the association causal and that appendicectomy – not appendicitis – exerted the effect; a further hypothesis is that factors that increase the risk of appendicitis reduce the risk of UC. Not enough is yet known, but it may be that the appendix has a role in balancing pro-inflammatory and anti-inflammatory T-cell responses.

What do you know about the pathology and distribution of UC?

UC is confined to the large bowel and always affects the rectum. A third of patients have pan-colitis, a third rectal (proctitis) or sigmoid disease only and a third colitis to the splenic flexure. Ulceration is usually superficial (mucosal). Granulomata are not a feature, and glands tend to be destroyed with crypt abscess formation, and the cellular infiltrate tends to comprise neutrophils, plasma cells and eosinophils.

What are the differential diagnoses of UC?

Infectious causes include *Yersinnia* spp. and mycobacterial disease. If there is a clear history of inflammatory symptoms (blood, mucus, pus or slime) that are not of infective origin (history and stool culture), IBD is very likely, usually UC but about 20% of CD is colitis. Sometimes, a nonspecific diagnosis of 'colitis' will be made, but the underlying cause will probably be IBD. Other possibilities include ischaemic colitis, microscopic colitis (watery rather than bloody diarrhoea), radiation colitis, drug-induced colitis – usually due to non-steroidal anti-inflammatory drugs with symptoms similar to UC but settling when withdrawn, diverticultis, irritable bowel syndrome, chronic pancreatitis and malabsorption, coeliac disease, sarcoidosis, rectal mucosal prolapse, small bowel cancer/lymphoma and colorectal cancer.

How is mild to moderate UC initially treated?

In active UC, prompt treatment can reduce the symptoms rapidly and reduce the risk of complications (Box 1.43).

5-ASA remains the mainstay of treatment for mild to moderate UC for the induction and maintenance of remission. By contrast, 5-ASA is at best only mildly effective in CD. 5-ASA has traditionally been taken in two or three daily doses but these regimens probably contribute to poor adherence and studies comparing the efficacy of once-daily mesalazine (and other newer formulations of 5-ASA) with divided doses support once daily dosing. Long-term 5-ASA reduces the increased risk of developing colorectal cancer associated with long-standing, extensive UC. Given the tolerability and safety of 5-ASA, attention has turned to using higher doses of mesalazine and overall increasing the dose of 5-ASA in active disease results in a moderate improvement in efficacy without a marked increase in side effects.

Corticosteroids remain one of the most effective ways of inducing remission. However, their inability to maintain remission and their serious side effect profile make their use unacceptable except for short periods.

Box 1.43 **Treatment of mild to moderate ulcerative colitis (UC)**

Topical treatment for distal colitis or proctitis

This may be treated with topical 5-aminosalicylic acid (5-ASA) or 'salicylate' therapy, e.g. mesalazine (suppository or enema). It is more effective than topical corticosteroid, but steroid suppositories or foam enemas (e.g. Predfoam, Colifoam) may be used and are better tolerated than liquid enemas (e.g. Predsol).

Systemic treatment

Corticosteroids are the most effective systemic treatment and are indicated if symptoms persist after 2 weeks, and can result in a remission rate of 75% within 2 weeks compared with 50–60% with 4–12 weeks' treatment with topical salicylate or steroid. For moderate attacks prednisolone 40 mg daily may be used for 1 week, then 30 mg daily for 1 week, then reduced over 6–8 weeks. For mild attacks prednisolone 20 mg may be used daily for 1 month, then reduced by 5 mg weekly.

Mild attacks

An effective alternative to corticosteroids for mild attacks is high-dose mesalazine, e.g. oral Pentasa 4 mg daily and suppository 1 g at night for a few weeks; 80% of patients respond.

Box 1.44 **Standard maintenance therapy in ulcerative colitis (UC)**

Salicylate choice depends on efficacy, side effect profile, serum concentration of 5-aminosalicylic acid and cost. The original was sulfasalazine (e.g. 2 g daily), but side effects include headaches, nausea and occasionally agranulocytosis and Stevens–Johnson syndrome. Newer salicylates are better tolerated and not associated with male infertility. Mesalazine in a coated preparation such as Asacol (1.2 g daily) or Pentasa microspheres (1.5 g daily) is most commonly used, but with caution in renal disease. Olsalazine (1 g daily) may cause watery diarrhoea but is useful if there is proximal constipation with distal disease. Corticosteroids have no role in maintenance of remission.

What is standard maintenance therapy in UC?

This is described in Box 1.44. The relapse rate is reduced from 80% to 20% at 1 year with salicylates. 5-ASA inhibits pro-inflammatory eicosanoid release from colonic epithelial cells, but nephrotoxicity is a potential side effect when absorbed.

Box 1.45 **Acute severe colitis**

Acute severe colitis in inflammatory bowel disease (IBD) has a natural mortality rate of 25% that is markedly reduced by surgery and corticosteroid treatment. It is, however, vital to recognise infection as a differential diagnosis or coexisting problem, and to know when there is steroid resistance and surgery is indicated.

Differential diagnoses

Acute colitis is caused by:

- Infection (32%)
- IBD (52%) – approximately one-fifth acute *de novo* IBD, four-fifths an IBD flare
- Other, e.g. acute ischaemia, non-steroidal anti-inflammatory drugs (NSAIDs), amphetamines.

Differentiating IBD from infection is key. Insidious onset and absence of fever favour IBD, whilst acute (< 7 days) onset, fever and high stool frequency (> 10 / day) favour infection. *Clostridium difficile*-associated diarrhoea is in the differential diagnosis, but now often coexists with IBD (usually without the classic pseudomembrane pattern) and *Clostridium difficile* colonisation greatly increases the risk of relapse of IBD. *Clostridium difficile* colonisation now affects 7–10% of hospital admissions and 20–30% of hospital inpatients.

Assessing severity

The Truelove and Witt criteria for acute colitis severity remain clinically helpful with admission to hospital indicated if stool frequency is > 6 / day together with one other criterion, and has prognostic implications:

- Bloody stool > 6 / day
- Fever 37.5°C
- Heart > 90
- Haemoglobin < 10.5 g / dl
- C-reactive protein (CRP) > 45

Management in the first 24 hours

- Stool microscopy, culture and sensitivity for bacteria (including *Clostridium difficile*), ova, cysts and parasites, and cytomegaolovirus (CMV) status for CMV colitis, now common, are mandatory.
- An abdominal X-ray is mandatory to exclude toxic megacolon (> 5.5 cm diameter) for which 75% of patients require surgery, and mucosal islands, which also determine a 75% need for surgery.
- Colonoscopy is needed if IBD is likely to determine severity and extent, if there is rectal sparing or confluent inflammation, or if mucosal islands are present.
- Antibiotics are clearly indicated for certain infections, e.g. *Clostridium difficile*, dysentery with *Shigella*, *Salmonella*, *Campylobacter*, amoebiasis.
- Corticosteroids are the most effective medical treatment for acute severe colitis due to IBD (intravenous with rectal hydrocortisone).
- Colectomy is needed in 12–20% of patients, rising to 40% if prior admission and 88% if previously on ciclosporin, with an overall rate of 20–30%. Toxic dilatation is treated medically for up to 24 hours but if no improvement occurs in stool frequency, colonic diameter or heart rate, urgent colectomy is indicated to avoid a 30% mortality rate associated with the risk of perforation.
- Intravenous fluids, electrolyte monitoring and thromboembolic prophylaxis are important.
- Antidiarrhoeal drugs (loperamide, opioids), antispasmodics / smooth muscle relaxants (Buscopan) and anticholinergics may provoke acute colonic dilatation and should be avoided, and NSAIDs can worsen colonic inflammation.

Management considerations thereafter

- If stool frequency remains > 8 / day or CRP is > 45 mg / l after 3 days of intensive therapy the options are infliximab and ciclosporin, or colectomy, made in conjunction with the medical and surgical team and the patient. Colectemy is certainly needed for perforation, toxic megacolon, severe haemorrhage or failed medical treatment, and is relatively low risk these days. Treatment that is becoming medically complex (e.g. a patient taking steroids, infliximab and ganciclovir) may be more safely served by surgery.
- After 5–7 days, approximately 40% will have a complete response, 30% an incomplete response treated thereafter as moderate colitis, and 30% may need or have had colectomy.

What is the approach to acute severe colitis?

This is outlined in Box 1.45.

What options are there for patients who have had an episode of severe colitis?

Patients who have had severe colitis should start azathioprine (2–2.5 mg / kg daily), e.g. for 3–5 years. Refractory severe colitis may be an indication for ciclosporin.

What options are there for patients with refractory UC?

Patients with moderate colitis who relapse with a dose of prednisolone reduced to under 15 mg or within 6 weeks of stopping prednisolone should start azathioprine as above. It is now standard practice to measure the activity of thiopurine methyltransferase (TPMT), an enzyme involved in thiopurine metabolism, before initiating treatment with azathioprine. This allows identification of the one in 300 people who will predictably develop bone marrow suppression due to deficiency of TPMT. Approximately 10% of people are *TPMT* heterozygotes (with intermediate activity) and require lower doses of thiopurines. Methotrexate is ineffective in UC, unlike CD. Refractory distal disease may respond to mesalazine suppositories (Pentasa 1 g at night) continued thrice weekly to maintain remission.

What are the indications for surgery in UC?

These include chronic symptoms (largest group), emergency surgery for severe colitis and dysplasia or colorectal carcinoma. Surgical options include subtotal colectomy with a remnant rectal stump and ileostomy, colectomy with an ileoanal pouch to avoid the need for ileostomy, ileorectal anastomois and panproctocolectomy with a permanent ileostomy.

When should colonoscopic surveillance be contemplated?

Colorectal cancer is more common with extensive and long-duration disease. The risk in patients with pancolitis is 5–10% at 15–25 years. Surveillance usually starts at 10 years. Long-term maintenance with aminosalicylates reduces the carcinoma risk.

What is microscopic colitis?

This is defined as a triad of chronic watery diarrhoea with normal colonoscopy and characteristic microscopic inflammation of the lamina propria. It is more common in older people. The term embraces collagenous colitis and lymphocytic colitis, and there is overlap between the two. Microscopic colitis has a mean age of incidence of 55–68 years and is uncommon (each entity one to five per 100 000/year) but is the final diagnosis in 10–15% of patients with chronic diarrhoea who present to specialist units. The cause is unclear, but luminal bacterial antigens may be important. Loperamide is useful for mild disease but budesonide and occasionally immunomodulatory therapy with azathioprine are needed for more severe disease.

CASE 1.42 ENTERIC AND URINARY STOMAS

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is a *percutaenous endoscopic gastrostomy (PEG)* tube *in situ* in this patient with obvious hemiparesis and dysphasia (Fig. 1.64).

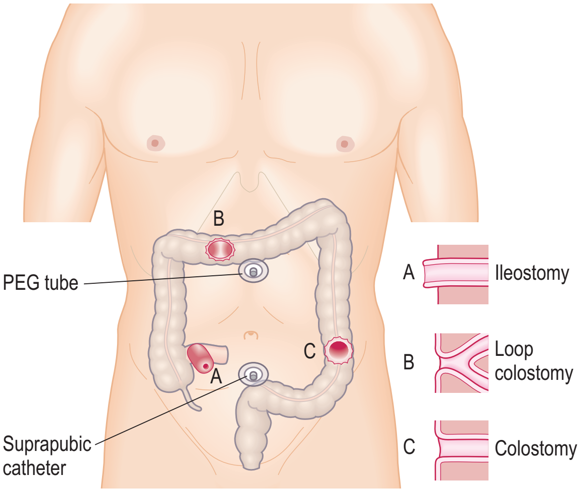


Figure 1.64 Percutaneous endoscopic gastronomy (PEG) tube and other surgical stomas. *(From Douglas, G., Nicol, F., Robertson, C., 2009. Macleod's Clinical Examination, Twelveth ed. with permission.)*

Interpretation

Confirm the diagnosis

This depends on the type of stoma.

What to do next – consider causes

The underlying diagnoses are wide. Most PEG tubes are inserted in patietns with chronic neurological disorders, notably stroke.

Consider severity/decompensation/complications

The risks and complications of PEG tubes are discussed in Case 4.34.

Consider function

Tell the examiners you would assess functional status following stroke rehabilitation.

Discussion

In which circumstances might a percutaenous endoscopic gastrostomy (PEG) tube be considered?

These are discussed in Case 4.34.

CASE 1.43 CARCINOID SYNDROME

Instruction

Please examine this patient's abdomen and briefly any other systems you think relevant before discussing your findings.

Recognition

There is *hepatomegaly* and *flushed skin*.

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about flushing and diarrhoea.

What to do next – assess other systems

Listen to the heart for right-sided murmurs.

Consider severity / decompensation / complications

Tell the examiners that the peptides causing carcinoid syndrome may cause:

- Bronchoconstriction – wheeze
- Increased gut motility – diarrhoea
- Endocardial fibrosis (a direct toxic effect of serotonin), notably right-sided valvular lesions, e.g. pulmonary stenosis, tricuspid regurgitation.

Carcinoid and other neuroendocrine tumours may also be part of multiple endocrine neoplasia (MEN) type 1.

Consider function

Carcinoid syndrome, unless specifically considered, can take considerable time to diagnose, promoting uncertainty and anguish.

Discussion

What are carcinoid tumours?

These are the most common neuroendocrine tumours, of enterochromaffin-like cells, and may arise from the foregut (stomach, pancreas, bronchus), midgut (duodenum to transverse colon) or hindgut (remaining colon); most commonly they are appendiceal.

What is carcinoid syndrome?

Most carcinoid tumours are non-functioning and asymptomatic. They may be found incidentally, e.g. in appendicectomy specimens. Their products, if functional, are metabolised by the liver. Symptoms are produced by release of serotonin, tachykinins and other vasoactive peptides into the circulation, known as carcinoid syndrome.

Why are liver metastases invariably present in carcinoid syndrome?

Efficient metabolism of peptides from the portal circulation by the liver usually suppresses symptomatic carcinoid syndrome. Hepatic metastases or situations where peptides are released directly into the systemic circulation as in bronchial carcinoid lead to symptoms.

How is carcinoid syndrome diagnosed?

This is by means of testing at least three 24-hour urine collections for detection of elevated 5-hydroxyindoleacetic acid, a metabolite of serotonin. Other hormones may be elevated, e.g. vasoactive intestinal peptide.

What may cause false-positive results?

Certain foods (e.g. banana, avocado, pineapple, plum, walnut, vanilla, aubergine) and certain drugs (e.g. paracetamol, naproxen, caffeine).

What investigations are needed if carcinoid syndrome is confirmed?

Imaging (CT or MRI) is the next step. Bowel imaging may be needed. Positron emission tomography with ^{11}C-5-hydroxytryptophan (a serotonin precursor) is a novel way of localising carcinoid tumours.

How would you manage carcinoid syndrome?

Antihistamines and loperamide may give symptomatic relief. Niacin supplementation may assuage tryptophan deficiency from the excessive serotonin synthesis in carcinoid syndrome that might otherwise cause pellagra. The mainstay of treatment if the tumour expresses somatostatin receptors is a somatostatin analogue such as octreotide, and radioisotope therapy with labelled octreotide is used to treat metastatic disease. Resection of a primary tumour or debulking of metastases may be considered. Debulking of tumour might also be achieved by transarterial embolisation, radiofrequency ablation or radiolabelled somatostatin analogues. Unhappily, the overall prognosis tends to be poor although the tumours are very slow growing.

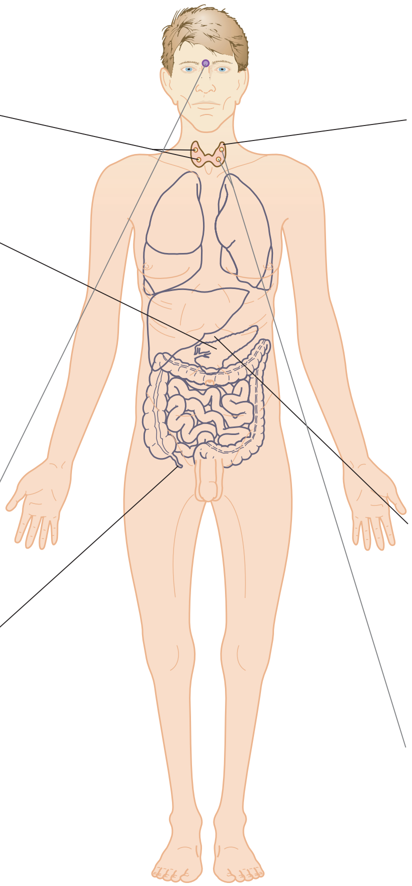
What are MEN syndromes?

These are tumours involving two or more endocrine glands. Diagnosis and management of each tumour are similar to those in non-MEN patients. MEN syndromes are outlined in Table 1.40.

Who should be screened for MEN syndromes?

By measurement of calcium, parathyroid hormone and anterior pituitary hormones, people who should be screened for MEN1 are any patient with two or more MEN1-associated tumours, a young adult with a single

Table 1.40 Multiple endocrine neoplasia (MEN) syndromes



MEN1	MEN2		
Chromosome 11q13 – probable tumour suppressor gene	Chromosome 10cen–10q11.2 containing c-ret proto-oncogene		
	MEN2a Most common MEN2	MEN2b	MTC only
Parathyroids (95%) ↑ PTH ↑ calcium	Medullary thyroid carcinoma ↑calcitonin	Medullary thyroid carcinoma ↑calcitonin	Medullary thyroid carcinoma ↑calcitonin
Pancreatic islets (40%) Gastrinoma ↑ gastrin and gastric acid Insulinoma ↑ insulin and hypoglycaemia Glucagonoma ↑ glucagons and glucose intolerance VIPoma ↑VIP and watery diarrhoea with hypokalaemia			
Pituitary (30%) Prolactinoma ↑ prolactin GH-secreting ↑ growth hormone ACTH-secreting ↑ cortisol	Phaeochromocytoma ↑catecholamines	Phaeochromocytoma ↑catecholamines	
Associated Carcinoid ↑5-HIAA Adrenal cortical ↑ cortisol Lipoma	Parathyroids ↑PTH ↑calcium	Associated Mucosal abnormalities Marfanoid habitus Medullated corneal nerve fibres Megacolon	

ACTH, adrenocorticotrophic hormone; GH, growth hormone; 5-HIAA, 5-hydroxyindoleacetic acid; MTC, medullary thyroid carcinoma; PTH, parathyroid hormone; VIP, vasoactive intestinal peptide.

MEN1 tumour or relatives of a patient with MEN1. People who should be screened for MEN2 are any patient with medullary thyroid carcinoma, any patient with two or more MEN2-associated tumours, a young adult with a single MEN2 tumour or relatives of a patient with MEN2.

CASE 1.44 CHRONIC MYELOID LEUKAEMIA

Instruction

Please examine this patient's abdominal system and discuss your findings.

Recognition

The spleen *is markedly enlarged* (Fig. 1.65). *Lymphadenopathy* may be present. Signs of bone marrow failure (*anaemia, petechial rash, signs of sepsis*) may be present.

Interpretation

Confirm the diagnosis

Confirm splenomegaly. The spleen enlarges towards the right iliac fossa and has a medial notch and it is not possible to feel its upper border. Measure enlargement in centimetres from the costal margin. Look for a bone marrow aspiration / trephine dressing or bruising over the iliac crest.

What to do next – assess other systems

Tell the examiners that you would ask about weight loss, fever, night sweats or abdominal pain (splenomegaly or splenic infarction), and request a peripheral blood film.

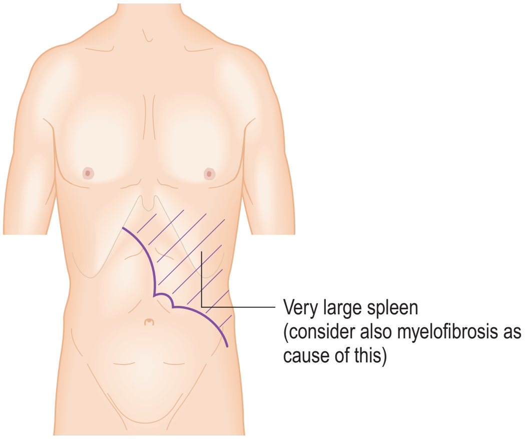


Figure 1.65 Chronic myeloid leukaemia.

Consider severity / decompensation / complications

Look for evidence of bone marrow failure (anaemia, fever, petechiae) (Fig. 1.66) or signs of immunosuppression from chemotherapy such as herpes zoster infection (Fig. 1.67).

Consider function

This very much depends on the stage of disease and its treatment, comorbidity and individual strategies for coping with it.

Discussion

What is the underlying genetic abnormality in chronic myeloid leukaemia (CML)?

In around 90% of patients there is a reciprocal translocation between chromosomes 9 and 22 to form a shortened chromosome 22, the Philadelphia (Ph) chromosome, which contains the chimeric gene *BCR/ABL*. *ABL*, an oncogene encoding a tyrosine kinase with dysregulated activity, is translocated from chromosome 9 to a specific

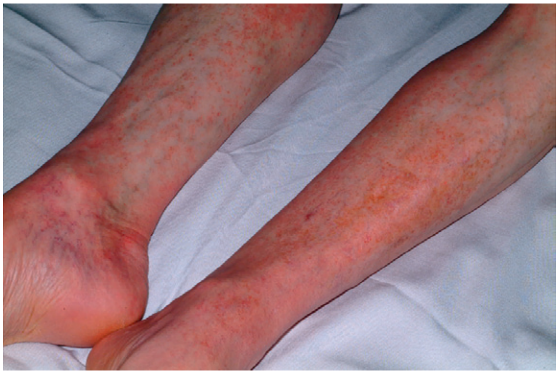


Figure 1.66 Petechial rash.

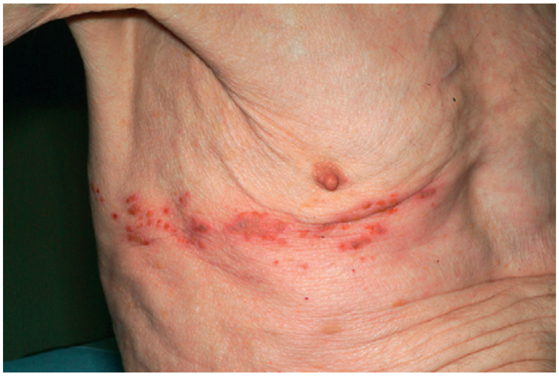


Figure 1.67 Herpes zoster.

breakpoint cluster region *BCR* on chromosome 22. Chimeric *BCR/ABL* mRNA encodes a protein with aberrant tyrosine kinase activity, which accelerates growth and differentiation of the myeloid line. This cytogenetic defect arises as a somatic defect within a single pluripotent haemopoietic stem cell (HSC) from which the clones of leukaemic cells are born. The defect usually arises spontaneously, but radiation (e.g. radiotherapy) is a known risk.

What is the difference between somatic and germline mutation?

Somatic mutation refers to mutation of genetic material within a particular cell and its clonal offspring. Germline mutation implies that every cell in the body carries the mutation. Somatic mutations underlie leukaemias and many malignancies.

What is the natural history of CML?

An initial chronic phase of clonal myelopoiesis (> 5% blasts) progresses inevitably to an accelerated phase with new cytogenetic changes (thought to arise from spontaneous acquisition of new cytogenetic changes, especially an extra Ph, trisomy 8 and iso-17q) and ultimately a terminal blastic phase. The natural history is to evolve within 3–5 years from the chronic phase to the advanced stage (accelerated phase or blastic transformation), which is rapidly fatal – some 6–24 months for the accelerated phase and under 6 months for the blastic phase, and the accelerated phase is sometimes even bypassed.

Box 1.46 **Treatment of chronic myeloid leukaemia (CML)**

- Treatment options before imatinib were limited to long-term administration of interferon (IFN)-α or allogeneic (from an HLA-identical donor) stem cell transplantation (SCT).
- Imatinib is a tyrosine kinase inhibitor (TKI), an oral inhibitor of BCR-ABL, acting through its ability to bind to the region of the ATP-binding site of the BCR-ABL protein. In 1999 it was shown to induce cytogenetic and clinical remission in patients not responding to IFN-α.
- Compared with allogeneic SCT, persistent leukaemia with the presence of BCR-ABL transcripts is evident in most patients treated with imatinib, but durability of response occurs in the majority of patients in the chronic phase, although not the accelerated phase. Thus TKI is standard treatment for most newly diagnosed with CML and newer generation TKIs (e.g. dasatinib, nilotinib) with much greater ability to inhibit BCR-ABL are increasingly used. Potential cure is possible with SCT, but carries significant morbidity and mortality.
- Mutation analysis should be performed in patients who fail to achieve complete haematological response at 3 months, or cytogenetic response at 18 months (with no decline in Philadelphia chromosome positivity) or who lose response to TKI treatment.
- Alkylating agents may be used for resistant CML, and combination chemotherapy, as for acute leukaemias, is appropriate for patients presenting in the accelerated phase, sometimes after a trial of TKI treatment.

How may CML be diagnosed?

CML is more common in middle-aged people. Around 50% of patients present when an abnormal blood film is detected as a chance finding, others often with non-specific symptoms. In the chronic phase a markedly raised white cell count (20×10^9 to $400 \times 10^9/l$) is typical. The peripheral blood film shows immature granulocytes with myelocytes and blasts. Basophils and platelets are often prominent. Vitamin B12 levels may be high. The bone marrow is hypercellular with loss of fat spaces. The *BCR/ABL* gene may be detected by fluorescence *in situ* hybridisation with specific fluorescent probes or by reverse transcriptase polymerase chain reaction (RT-PCR). In the accelerated phase the white cell count increases, with anaemia, thrombocytosis or thrombocytopenia. In the blast phase, blasts or blasts and promyelocytes take over the bone marrow and spill liberally into the blood.

How is CML treated?

Treatments target the chronic phase, because normal stem cells are replaced by Philadelphia-positive stem cells as CML progresses, and are outlined in Box 1.46.

How are patients with CML monitored?

Patients responding to tyrosine kinase inhibitor (TKI) treatment or in complete remission after stem cell transplantation are best monitored by measuring *BCR/ABL* transcripts using RT-PCR. This allows detection of minimal residual disease, early detection of relapse and assessment of cytogenetic responsiveness to treatment. Further, cytogenetic techniques can monitor cytogenetic changes heralding blast transformation.

What are HSCs and how do they become mature cells?

HSCs have the capacity for self-renewal and are pluripotent. They live in the bone marrow where they divide and differentiate into populations of progenitor cells committed to each of the main marrow cell lines.

Cell differentiation is directed by haemopoietic growth factors such as granulocyte–colony-stimulating factor (G-CSF), thrombopoietin and erythropoietin, all lineage specific.

Proerythroblasts are large with dark-blue cytoplasm and primitive nuclear material or chromatin. As they differentiate they become smaller, with increasing amounts of haemoglobin and polychromatic cytoplasm as chromatin condenses. The nucleus is eventually extruded, giving rise to a reticulocyte. Reticulocytes still contain RNA and are capable of haemoglobin synthesis, but spend only a few days in the marrow before travelling to the spleen where they lose RNA and become fully fledged erythrocytes.

Whilst the marrow is the primary site of granulocyte (neutrophil, eosinophil, basophil) and lymphocyte formation, most circulating mature lymphocytes are produced after migration to peripheral secondary lymphoid tissue (lymph nodes, spleen, thymus and gastrointestinal associated lymphoid tissue). Lymphocytes normally constitute < 10% of marrow cells. Plasma cells are typically basophilic cells with a blue tinge and eccentric nucleus. Large numbers of neutrophils are held in reserve in the marrow. Those that enter the circulation spend only hours within it before adhesion and migration into the tissues under the influence of chemokines. Of the circulating pool, about half are loosely adherent to the endothelium, a phenomenon called margination. Monocytes may survive for months or even years in tissues as macrophages or as antigen-presenting cells.

How may bone marrow examination aid diagnosis in haematological disease?

Bone marrow aspirates may be examined for morphology of cells and differential counts, the presence of abnormal cells such as leukaemic, metastatic or infective cells, and organisms and iron status. Bone marrow trephines provide cores of bone and marrow for histological assessment, useful for examining marrow architecture and cellularity and are the most reliable way of detecting marrow infiltrates.

List some causes of neutrophilia and neutropenia

Neutrophilia is common in bacterial infection and physiological stress (e.g. acute coronary syndrome); corticosteroids induce demargination – removal of marginated or adhered neutrophils on the endothelium, the latter a normal situation such that the normal laboratory range for neutrophils underestimates the real number. Neutropenia may be seen in overwhelming sepsis, chemotherapy, myelodysplasia and bone marrow infiltration from leukaemia, myeloma, lymphoma, myelofibrosis or secondary carcinoma. All cytopenias may be classified into either increased peripheral destruction / utilisation (there may be a compensatory bone marrow response as in sepsis, when the bone marrow response causes a left-shifted peripheral blood film) or deficient marrow production.

What is demargination?

This is the process in which neutrophils adherent to the endothelium slip off it, commonly induced by corticosteroid therapy to cause an approximate doubling in the laboratory neutrophil count.

What is leucoerythroblastic change?

This refers to the presence of nucleated red cells and white cell precursors in peripheral blood. It is seen in severe illness such as sepsis or trauma and in marrow infiltration.

How do acute leukaemias differ from chronic leukaemias?

Acute leukaemias are characterised by their rapid onset and their high proportion of undifferentiated blast cells compared with chronic leukaemias, due to early progenitor cell as opposed to more mature cell immortalisation. Aberrant myeloid or lymphoid precursors arise in the bone marrow after somatic mutation of a single cell and spill into the blood. Blast cells on a peripheral blood film often provide initial evidence of suspected acute leukaemia. Clinical features of acute leukaemias result from the consequences of bone marrow failure (neutropenia – mouth ulcers, pneumonia; thrombocytopenia – purpura; anaemia) and organ infiltration (lymph nodes, spleen, liver, meninges, testes (especially acute lymphoblastic leukaemia), skin and gums (some acute myeloid leukaemias)). Chronic lymphocytic leukaemia arises from mature lymphocyte precursors. CML is a stem cell disorder in which differentiation is possible. Acute myeloid leukaemia (AML) represents a more mature but arrested stage.

How is AML classified?

AML may be classified morphologically using the French American British (FAB) classification (Table 1.41) to distinguish subtypes based on cell appearance and cytochemistry staining, immunologically using monoclonal antibodies to cell surface markers, or cytogenetically. It is evident that the most important prognostic indicator is the specific mutation within a leukaemic clone and cytogenetic methods are used to define specific subtypes and guide treatment.

What are Auer rods?

Auer rods are aggregates of granules seen in M1, M2 and especially M3 stages of AML.

What is acute promyelocytic leukaemia (APML)?

APML is the result of the fusion of the *PML* gene on chromosome 15 with the *RARα* gene on chromosome 17 to form the APML t(15;17) PML/RARα fusion proto-oncogene and protein that interferes with factors essential for normal differentiation of myeloid precursors. APML cells contain procoagulant 'junk' material. Cell lysis can cause disseminated intravascular coagulation (DIC). All-*trans* retinoic acid stabilises coagulopathy and induces differentiation of promyelocytes and may be used to induce remission in the absence of chemotherapy without causing DIC. Post-induction chemotherapy is needed to maintain remission.

What are the treatment principles in AML?

Remission induction is followed by consolidation therapy (better than low-dose maintenance) with agents such as cytarabine and an anthracycline. Non-intensive treatment

Table 1.41 French American British (FAB) classification of acute myeloid leukaemia

FAB classification	Subtype	Features
M0	Acute myeloblastic leukaemia with minimal differentiation	Least differentiated, with large, agranular myeloblasts
M1	Acute myeloblastic leukaemia without maturation	Blasts constitute ≥ 90% of nucleated (non-erythroid) cells
M2	Acute myeloblastic leukaemia with maturation	Blasts 30–89% but definite promyelocyte differentiation
M3	Acute promyelocytic leukaemia	Mostly abnormal promyelocytes, containing granules of procoagulant material
M4	Acute myelomonocytic leukaemia	An eosinophilic subtype is recognised
M5	Acute monocytic/monoblastic leukaemia	Monoblasts, promonocytes or monocytes constitute > 80% of nucleated cells
M6	Acute erythroleukaemia	Erythroid component of marrow constitutes > 50% of cells
M7	Acute megakaryoblastic leukaemia	
M8	Acute basophilic leukaemia	

in older people may include hydroxycarbamide. Stem cell transplantation is potentially curative. Supportive therapy includes blood products, antimicrobials for febrile neutropenia, and haemopoietic growth factors. A temperature > 38.3 °C with neutropenia should prompt immediate broad-spectrum antimicrobials with staphylococcal cover if an invasive *Hickman* line is *in situ*. Fever for a few days should prompt antifungal cover, not least for invasive pulmonary aspergillosis. In contrast to CML, the molecular complexity of AML means that targeting molecular therapies against tyrosine kinases and other pathways is more challenging, other than treatment for APML.

Why have leukaemia outcomes improved in recent years and what predictors are there of prognosis?

Leukaemia outcomes have improved as a result of improved chemotherapy, stem cell transplantation and improved supportive care. Further, increased understanding of the molecular basis of individual leukaemias has allowed more targeted therapies. Predictors of prognosis are outlined in Table 1.42.

Table 1.42 Predictors of prognosis in acute leukaemias

Age	Older people generally have a very poor prognosis with AML, probably reflecting pre-existing myelodysplasia, drug resistance genes and generally adverse cytogenetics, as well as poor tolerance to treatment
Bone marrow cytogenetics	T(8;21), t(15;17), and inv(16) confer a favourable prognosis Adverse cytogenetics in people over 70 years produce a 1-year survival with intensive chemotherapy of under 10%
Molecular profile	FLT3 tyrosine kinase (poor prognosis), NPM1 and CEBPA
Initial response to chemotherapy	Better prognosis if achieve complete remission
Comorbidities	Better if no cardiac or respiratory disease
Presentation white count	Poor prognosis if $> 100 \times 10^9$ / l in AML

AML, acute myeloid leukaemia.

What are the principles of bone marrow or haemopoietic stem cell transplantation (HSCT)?

HSCT involves harvesting stem cells from donor marrow or more commonly peripheral blood (the stem cell content of blood being augmented by chemotherapy and G-CSF before harvest) and using these to repopulate and regenerate recipient marrow, thus rescuing the recipient from aplasia. HSCT relies on the fact that stem cells infused into the peripheral vein of a recipient 'home' to the marrow to re-establish haemopoiesis. Donors may be autologous (same patient) or allogeneic (HLA-matched relative or unrelated donor).

A specific concern with autologous transplantation is the potential for tumour cells to contaminate the graft, and numerous purging techniques have been used in attempts to reduce rates of disease relapse. HSCT, in conjunction with intensive supportive therapy until the infused stem cells are able to produce adequate numbers of red and white cells and platelets, allows the use of high-dose chemotherapy in recipients. Supportive therapy includes blood products, growth factors and antimicrobials.

In which conditions is HSCT considered?

HSCT can be used in AML, acute lymphoblastic leukaemia, CML, chronic lymphoblastic leukaemia, myelodysplasia, lymphoma, myeloma and non-malignant disorders including severe aplasia. HSCT for breast cancer has not proven beneficial and there is not yet evidence for benefit in other solid tumours.

What is graft versus host disease?

In allogeneic transplants donor and recipient are not immunologically identical and so activation of donor lymphocytes occurs against host antigens. This may cause immune damage to the skin, gut and liver of the recipient. However, a graft versus tumour effect may also occur, donor lymphocytes recognising and eliminating residual malignant cells in the recipient. This has led to interest in donor lymphocyte infusion for antimalignancy effects, notably in CML.

Do stem cells from other tissues have a role in medicine?

Of emerging interest is the use of stem cells from other tissues to repair diseased or degenerating tissue. Stem cells may have the ability to transdifferentiate ('plasticity'), and it may be possible to redirect stem cells from muscle, brain, skin, liver and other sites to differentiate into tissue different from that originally intended.

CASE 1.45 POLYCYTHAEMIA VERA, MYELOPROLIFERATIVE DISORDERS AND MYELODYSPLASIA

Instruction

This man reports pruritus after a hot bath. Please examine his abdomen and report your findings.

Recognition

There is *moderate splenomegaly*. There may be facial plethora, suffusion of the conjunctivae and engorgement of retinal vessels.

Interpretation

Confirm the diagnosis

The median age of presentation is 55–60 years. Polycythaemia vera (PV) may present with the symptoms listed in Box 1.47. Tell the examiners that you would ask about these symptoms, but in fact the classic presentation of splenomegaly and itch is uncommon.

Box 1.47 **Possible symptoms of polycythaemia vera**

- Headaches
- Lethargy
- Dyspnoea
- Weight loss
- Night sweats
- Pruritus (exacerbated by a hot bath)
- Left upper quadrant pain (splenomegaly)
- Gout

What to do next – consider causes

Tell the examiners about differentiating the types of polycythaemia (erythrocytosis):

- Erythrocytosis is defined as a packed cell volume (PCV) > 0.51 in men and > 0.48 in women, and these, or haemoglobin concentrations respectively of > 17 and > 15 g/dl, warrant further evaluation.
- A red cell mass (RCM) study determines whether erythrocytosis is absolute (increased RCM) or apparent (normal RCM, reduced plasma volume). Absolute may be assumed if PCV is ≥ 0.60 in men or ≥ 0.56 in women.
- If absolute, further tests are needed to differentiate between PV, secondary erythrocytosis and idiopathic erythrocytosis (Fig. 1.68). Exclusion of secondary causes may include oximetry, chest X-ray, renal and liver function tests, serum erythropoietin levels (suppressed in PV), abdominal imaging and sleep studies.

To confirm PV, the PV Study Group (in guidelines prepared by the British Committee of Standards in Haematology 2005) proposes the criteria listed in Table 1.43 and the World Health Organization (WHO) proposes similar criteria.

Diagnosis may now be made by identification of a specific JAK2 mutation in around 90% of cases of PV, rendering bone marrow aspiration increasingly unnecessary. The acquired mutation, JAK2 V617F, affects an exon on the Janus Kinase 2 gene. JAK2 is a tyrosine kinase that transduces signals from erythropoietin. Mutated JAK2 is constitutively active, leading to increased downstream signalling and dysregulation of haematopoiesis. Many JAK2 V617F-negative patients have an alternative exon (usually 12) at fault.

Consider severity/decompensation/complications

Vascular thromboses, particularly arterial, and occasionally bleeding, are the major clinical events. Tell the examiners that you would ask about strokes and priapism. Other complications include erythromelalgia (red, burning feet and fingers), hepatosplenomegaly, peptic ulceration, gout and leukaemic transformation.

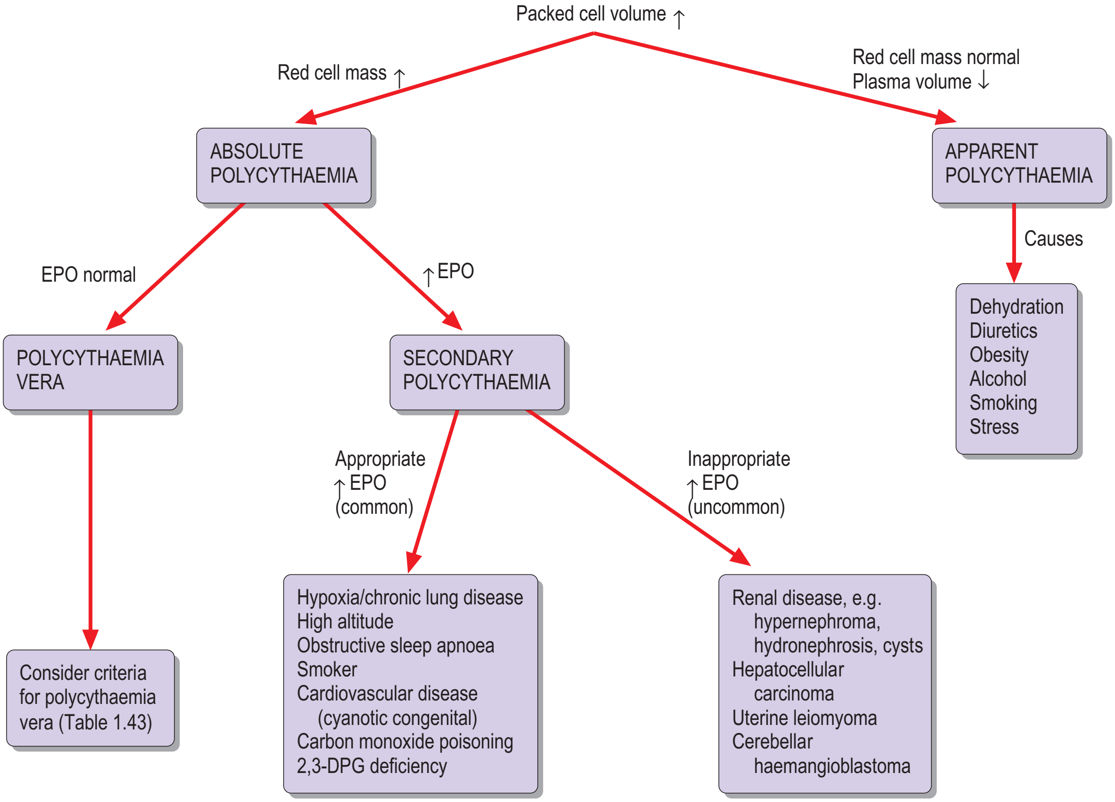

Packed cell volume ↑
Red cell mass ↑
Red cell mass normal
Plasma volume ↓
ABSOLUTE POLYCYTHAEMIA
APPARENT POLYCYTHAEMIA
Causes
Dehydration
Diuretics
Obesity
Alcohol
Smoking
Stress
EPO normal
↑EPO
POLYCYTHAEMIA VERA
SECONDARY POLYCYTHAEMIA
Appropriate ↑EPO (common)
Inappropriate ↑EPO (uncommon)
Consider criteria for polycythaemia vera (Table 1.43)
Hypoxia/chronic lung disease
High altitude
Obstructive sleep apnoea
Smoker
Cardiovascular disease (cyanotic congenital)
Carbon monoxide poisoning
2,3-DPG deficiency
Renal disease, e.g. hypernephroma, hydronephrosis, cysts
Hepatocellular carcinoma
Uterine leiomyoma
Cerebellar haemangioblastoma

Figure 1.68 Scheme for assessing causes of polycythaemia. DPG, diphosphoglycerate; EPO, erythropoietin.

Table 1.43 Criteria for polycythaemia vera (PV): PV diagnosed by A1 and A2, plus A3 or A4 or any two of B

Major criteria	Minor criteria
A1 RCM absolute increase or if RCM unavailable haematocrit ≥ 0.60 in males or ≥ 0.56 in females (WHO guidelines allow haemoglobin concentration)	B1 Thrombocytosis (50% of patients)
A2 No secondary cause	B2 Neutrophil leucocytosis (two-thirds of patients)
A3 Palpable spenomegaly (WHO guidelines do not stipulate palpable)	B3 Splenomegaly detected by scanning (WHO guidelines suggest marrow biopsy)
A4 Clonality marker (acquired abnormal marrow karyotype) other than Ph chromosome or *bcr / abl* fusion gene	B4 Characteristic growth of burst-forming units, erythroid, or reduced serum erythropoietin

Ph, Philadelphia; RCM, red cell mass; WHO, World Health Organization.

Classically there are two phases of PV: an initial proliferative polycythaemic phase and a spent or post-polycythaemic phase in which cytopenias are associated with ineffective haemopoiesis, marrow fibrosis, extramedullary haemopoiesis and splenomegaly.

Consider function

The symptoms and complications can be very disabling. Tell the examiners that it is imperative to recognise and treat PV before thrombotic complications ensue.

Discussion

How is polycythaemia vera (PV) managed?

Thrombosis is the leading cause of death, with a median survival of 18 months in untreated patients extended to 8–15 years with treatment. Control of the elevated PCV is by venesection or cytoreductive therapy (especially if thrombocytosis) with hydroxyurea (hydroxycarbamide). The latter might increase the risk of leukaemia, but not as much as the historically used phosphorus and busulfan. Interferon-γ and anagrelide are new treatments, without leukaemogenic risk, again tending to be used with associated thrombocytosis. The target PCV is 0.45 and platelets $400 \times 10^9/l$. Antiplatelet agents (aspirin) are beneficial if

Box 1.48 Myeloproliferative disorders

- Polycythaemia vera
- Essential thrombocythaemia
- Primary myelofibrosis
- Chronic myeloid leukaemia

there are no contraindications such as bleeding or a very high platelet count (> 1500 × 10^9/l), which can cause paradoxic bleeding.

What may PV transform to?

PV may transform to myelofibrosis (spent phase, occurring in 15–20% of patients at 10 years) characterised by progressive splenomegaly and pancytopenia and generally treated supportively, or AML (5% at 10 years), a terminal feature of any myeloproliferative disorder (MPD) and refractory to treatment.

What are MPDs?

These are clonal stem cell disorders characterised by proliferation of one or more of the erythroid, granulocytic or megakaryocytic cell lines with excess red cells, white cells or platelets in peripheral blood. There is often overlap of erythropoietic, granulopoietic and megakaryocytic expansion, lending support to the notion of a clonal stem cell defect. Cells are morphologically normal, although the WHO classification now recognises overlap with myelodysplastic syndromes. The main MPDs are listed in Box 1.48.

Rare MPDs include chronic neutrophilic and eosinophilic leukaemia.

What do you know about essential thrombocythaemia (ET)?

ET causes clustering of megakaryocytes in marrow and persistent thrombocytosis (>600 × 10^9/l is generally accepted for diagnosis). It results in thrombosis and bleeding and, longer term, myelofibrosis (10% at 10 years) or AML (1–2% at 10 years). Diagnosis is by exclusion of other MPDs and reactive thrombocytosis (iron deficiency anaemia, bleeding, inflammation – rheumatoid arthritis/inflammatory bowel disease, malignancy). The JAK-2 mutation is found in around 50% of patients. Haemorrhage occurs with very high platelet counts (> 1500 × 10^9/l). Most patients benefit from aspirin and hydroxycarbamide. Alternatives include phosphorus and busulfan, both leukaemogenic, or interferon and anagrelide.

What do you know about primary myelofibrosis (PMF)?

PMF may arise *de novo*, or as a late phase of PV or ET. The JAK2 mutation is found in around 50% of patients, and sometimes the MPL W515L/K mutation. Fibrosis may occur because diseased megakaryocytes release mitogens such as growth factors directly stimulating fibroblast proliferation. Median presentation is at 50–60 years with symptoms relating to marrow failure or splenomegaly. Diagnosis is by splenomegaly, marrow histology (coarse parallel reticulin and later osteomyelofibrosis), a leucoerythroblastic blood film, often with tear-drop cells, absence of other MPDs and exclusion of secondary myelofibrosis. Progression to AML occurs in 25% of patients and overall prognosis in PMF is poor.

What are myelodysplastic syndromes?

It has long been known that some leukaemias smoulder for a long time before becoming clinically apparent, and that some unusual anaemias transform to acute leukaemia. Myelodysplasia refers to a group of clonal disorders of haemopoietic stem cells, which retain the ability to differentiate into mature cells, but do so in a disordered and ineffective manner. This leads to hypercellular bone marrow and peripheral blood cytopenia.

How do myelodysplastic syndromes arise?

They are caused by cumulative acquisition of cytogenetic errors, e.g. deletions of tumour suppressor genes on chromosomes 5 and 7 have been implicated. This causes the neoplastic clone to divide more rapidly, but the resultant haemopoiesis is ineffective with a high rate of apoptosis. As cytogenetic errors accumulate, the clone becomes less stable, myeloblasts accumulate and acute leukaemia ensues.

How are myelodysplastic syndromes classified?

Various classifications have been used (e.g. WHO, Table 1.44), and are contentious as the aetiology of these syndromes is not well understood and considerable overlap occurs.

How are myelodysplastic syndromes diagnosed?

They are uncommon before 60 years of age. Patients are usually asymptomatic but may present with anaemia, bleeding, recurrent infections or mouth ulcers. Chronic myelomonocytic leukaemia may cause hepatosplenomegaly and when monocytes are too abundant and become tissue macrophages this can lead to gum hypertrophy, pleural or pericardial effusions, arthritis or skin lesions. Peripheral blood abnormalities in myelodysplastic syndromes may include the presence of the following cells or phenomena: macrocytes, aniso-poikilocytes, a dimorphic picture, polychromasia, basophilia, normoblasts, reticulocytopenia, hypogranular neutrophils, hypersegmented neutrophils, mono- or bilobed neutrophils, monocytosis, promonocytes, agranular platelets, giant platelets and megakaryocyte fragments. Marrow abnormalities may include erythroid hyperplasia, multinuclear red cell precursors, ring sideroblasts, hypogranularity of myeloid precursors, increased promonocytes, blasts and abnormal

Table 1.44 World Health Organization classification of myelodysplastic syndromes (simplified)

Refractory cytopenia with unilineage dysplasia (refractory anaemia, refractory neutropenia, refractory thrombocytopenia)
Refractory anaemia with ring sideroblasts (RARS)
Refractory anaemia with ring sideroblasts – thrombocytosis (RARS-t) – a myelodysplastic / myeloproliferative disorder usually having a JAK2 mutation
Refractory cytopenia with multilineage dysplasia
Refractory anaemia with excess blasts I and II
Acute leukaemia 5q–syndrome (typically older women with normal or high platelet counts and isolated deletions of the long arm of chromosome 5 in bone marrow cells)
Myelodysplasia unclassifiable
Chronic myelomonocytic leukaemia – now removed from the myelodysplastic syndrome classification and categorised as a myelodysplastic–myeloproliferative overlap syndrome

Box 1.49 **Treatments for myelodysplastic syndromes**

- Supportive care (blood transfusion for symptomatic anaemia with iron chelation therapy – without chelation 60 units usually leads to iron overload and 100 units leads to cardiac damage, platelet transfusions for bleeding and prompt treatment of febrile neutropenia)
- Erythropoietin 150–300 U / kg subcutaneously three to seven times weekly as an alternative +/– granulocyte–colony-stimulating factor
- Allogeneic stem cell transplantation (the only curative option)
- Intensive chemotherapy (for younger patients)
- Epigenetic therapy (azacitidine and decitabine reduce DNA methylation and offer low-intensity treatment that may significantly improve survival)
- Immunosuppression (some evidence for an immune process in pathogenesis – antithymocyte globulin or ciclosporin in selected cases). Lenalidomide and other immunomodulatory drugs may be used in 5q–syndrome

megakaryocytes. Cytogenetic chromosomal analysis is helpful. Serum B12 levels may be high. The differential diagnosis includes other causes of cytopenias, e.g. acute leukaemia, aplastic leukaemia, immune thrombocytopenia, marrow infiltration, acquired immunodeficiency syndrome.

What is the treatment for myelodysplastic syndromes?

Treatments are listed in Box 1.49.

What is the prognosis in myelodysplastic syndromes?

Several prognostic scoring systems have been devised, and > 5% blasts is associated with shorter survival. Around a third of patients die from acute leukaemia, a third from cytopenia and a third from unrelated causes.

What do you understand by the term bone marrow failure?

Bone marrow failure refers to primary failure, at a HSC level, to produce one or more cell lineages. The term usually excludes pancytopenia associated with marrow infiltration as in leukaemias and cytopenias, and conditions arising from peripheral destruction.

What is acquired aplastic anaemia (AA)?

This is a rare disease comprising: peripheral pancytopenia; hypocellular marrow, but with morphologically normal cells; replacement of normal haematopoietic cells by fat cells without an increase in reticulin or fibrosis; no evidence of a malignant or other cause. The differential diagnosis includes malignancy (acute leukaemia, hypoplastic myelodysplastic syndrome), autoimmune pancytopenia, toxicity from chemotherapy or radiotherapy and inherited causes such as Fanconi's anaemia.

What causes AA?

The cause is usually unknown except where a specific drug (there are many!), virus (e.g. parvovirus B19, notable for causing red cell aplasia), chemical or unusual association (e.g. paroxysmal nocturnal haemoglobinuria) can be implicated. An immune pathogenesis probably results in suppression of recovery of damaged cells; cytokines such as tumour necrosis factor-α and interferon-γ upregulate the expression of stem cell receptors that trigger apoptosis.

How is AA investigated?

Anaemia, bleeding or infection can bring it to attention. It is classified as:

- Very severe (neutrophils $< 0.2 \times 10^9$ / l, platelets $< 20 \times 10^9$ / l, reticulocytes $< 20 \times 10^9$ / l, transfusion dependent)
- Severe (neutrophils 0.2×10^9 to 0.5×10^9/l, otherwise as for very severe)
- Non-severe (neutrophils 0.5×10^9 to 1.5×10^9 / l, platelets 20×10^9 to 100×10^9/l, reticulocytes 20×10^9 to 60×10^9 / l).

Lymphocyte numbers may be preserved and neutrophils are heavily granulated. Bone marrow examination, which is usually easily obtained, reveals hypocellularity and a 'lacy' appearance, but changes are patchy. Cytogenetic studies on marrow aspirates may show abnormal but stable clones, previously thought to indicate myelodysplastic syndromes, although distinction between AA and hypoplastic myelodysplastic syndromes can be difficult. Peripheral blood lymphocytes may be examined for chromosome breaks characteristic of Fanconi's anaemia.

How is AA managed?

Supportive measures may be followed by immunosuppression with antithymocyte globulin via a central vein together with ciclosporin. Allogeneic stem cell transplantation may be considered.

What other bone marrow failure syndromes are there?

These include pure red cell aplasia (often associated with viruses, drugs or autoimmune diseases), amegakaryocytic thrombocytopenia and cyclical neutropenia.

CASE 1.46 CHRONIC LYMPHOCYTIC LEUKAEMIA

Instruction

Please examine this 75-year-old man's lymphoreticular system and discuss your findings.

Recognition

There is widespread *lymphadenopathy* and moderate *splenomegaly / hepatosplenomegaly* (Fig. 1.69). Lymph nodes are often markedly enlarged, painless and rubbery.

Interpretation

Confirm the diagnosis

Tell the examiners that you would request a peripheral blood film. This would demonstrate an excess of small, mature lymphocytes with smear / smudge cells (broken *in vitro* by slide preparation), pathognomonic of chronic lymphocytic leukaemia (CLL) and differentiating it from other lymphoproliferative disorders.

What to do next – assess other systems

Tell the examiners that you would ask about symptoms. B symptoms such as sweats and weight loss are uncommon.

Consider severity / decompensation / complications

You could mention staging, prognosis and complications.

Staging

Clinical staging is important for prognosis, and assesses organ involvement and cytopenias. The Rai classification is shown in Box 1.50.

The alternative Binet classification considers three stages: A if between zero and two organs are involved, haemoglobin > 10 g / dl and platelets > 100 × 10^9 / l, B if three to five organs are involved with the same blood parameters and C if blood parameters are low.

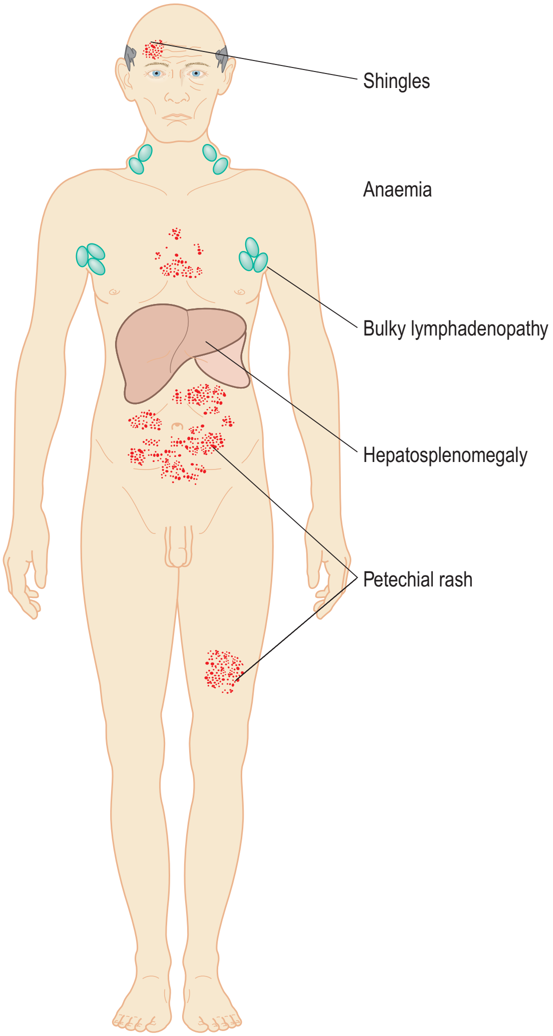


Figure 1.69 Chronic lymphocytic leukaemia.

Box 1.50 Rai classification

- 0 Lymphocytosis
- I Lymphocytosis + lymphadenopathy
- II Lymphocytosis + splenomegaly and/or hepatomegaly
- III Lymphocytosis + anaemia (haemoglobin < 11 g / dl)
- IV Lymphocytosis + thrombocytopenia (platelets < 100 × 10^9 / l)

Prognosis and complications

Prognostic indicators and complications in CLL are shown in Table 1.45.

Consider function

This very much depends on the stage of disease and its treatment and comorbidity (CLL tends to affect older people).

Table 1.45 Prognostic indicators in chronic lymphocytic leukaemia (CLL)

Mutational status	B cells rearrange the immunoglobulin heavy chain variable region to produce antibodies, and this includes a step in which somatic mutation occurs after the B cell has moved through the germinal centre early in its development – a better prognosis (20-year median survival) is possible if somatic mutations are detected since these indicate a more mature, differentiated clone
Cytogenetics	50% of CLLs have a small deletion on chromosome 13 indicating a good prognosis 25% of CLLs have a small deletion on chromosome 11q23 indicating a poor prognosis A 17p deletion at p53 confers resistance to conventional treatments such as alkylating agents and purine analogues and a very poor prognosis and aggressive treatment with high-dose steroids and alemtuzumab may be considered
Autoimmune disease	Autoimmune haemolysis and thrombocytopenia are common in CLL; anti-CD20 antibody (rituximab) may be indicated
Transformation	Transformation to diffuse large B-cell lymphoma or Richter's syndrome may occur Epstein–Barr virus-related transformation is more common now because of immunosuppression induced by purine analogue treatment
β_2-microglobulin	This is an indicator of lymphocyte turnover and load, and may also be used to assess treatment response
Immunosuppression	The leukaemic B-lymphocyte clone suppresses the normal B-lymphocyte population, causing immune deficiency, but T-cell dysregulation also contributes Herpes zoster virus reactivation is very common

Discussion

What is the underlying defect in chronic lymphocytic leukaemia (CLL)?

CLL is the most common chronic leukaemia in the Western world, and tends to occur in older people, more so in men. A range of mutations is possible, arising in mature B-lymphocyte precursors, with differing prognoses. The pathogenesis is uncertain. Trisomy 12 and chromosome 13 deletions are common but secondary to the primary event. In some young patients a deletion in chromosome 11 is associated with CLL and ataxia–telangiectasia. Around half of patients with CLL have somatic mutations in the immunoglobulin heavy-chain variable region genes and half do not, suggesting that CLL starts with disease in a germinal centre cell that has encountered an antigen in the former and in a naive cell in the latter.

How is diagnosis confirmed?

Immunophenotyping for the cluster designation (CD) surface marker profile of blood or bone marrow clonal cells is diagnostic. CLL cells express CD23 and CD5. Routine investigations in the work-up of CLL and exclusion of differential diagnoses include haemobiochemistry, bone marrow examination, immunoglobulins, Coomb's test and abdominal computed tomography scan.

When should CLL be treated?

Treatment is for symptomatic disease, aiming to decrease tumour cell load, because CLL is not curable. The long natural history means that many patients remain asymptomatic and die from an unrelated problem.

Box 1.51 **Treatment of chronic lymphocytic leukaemia**

- First-line treatment is with alkylating agents (chlorambucil) and fludarabine (a purine analogue) as combination chemotherapy. Steroids may improve marrow reserve and are considered if there is cytopenia.
- Rituximab (anti-CD20) may be used.
- Allogeneic stem cell transplant is considered in younger patients and more aggressive therapies, including lenalidomide and alemtuzumab (anti-CD52), in patients with refractory disease.
- Splenectomy, splenic irradiation and leukapheresis may be used for bulky splenomegaly or cytopenias. Supportive treatments include antimicrobials, allopurinol and haemopoietic growth factors.

How is CLL treated?

Treatments are listed in Box 1.51.

CASE 1.47 LYMPHADENOPATHY AND LYMPHOMA

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is *painless lymphadenopathy* (often widespread and not necessarily contiguous) and *hepatosplenomegaly*.

Other features may be present (Fig. 1.70).

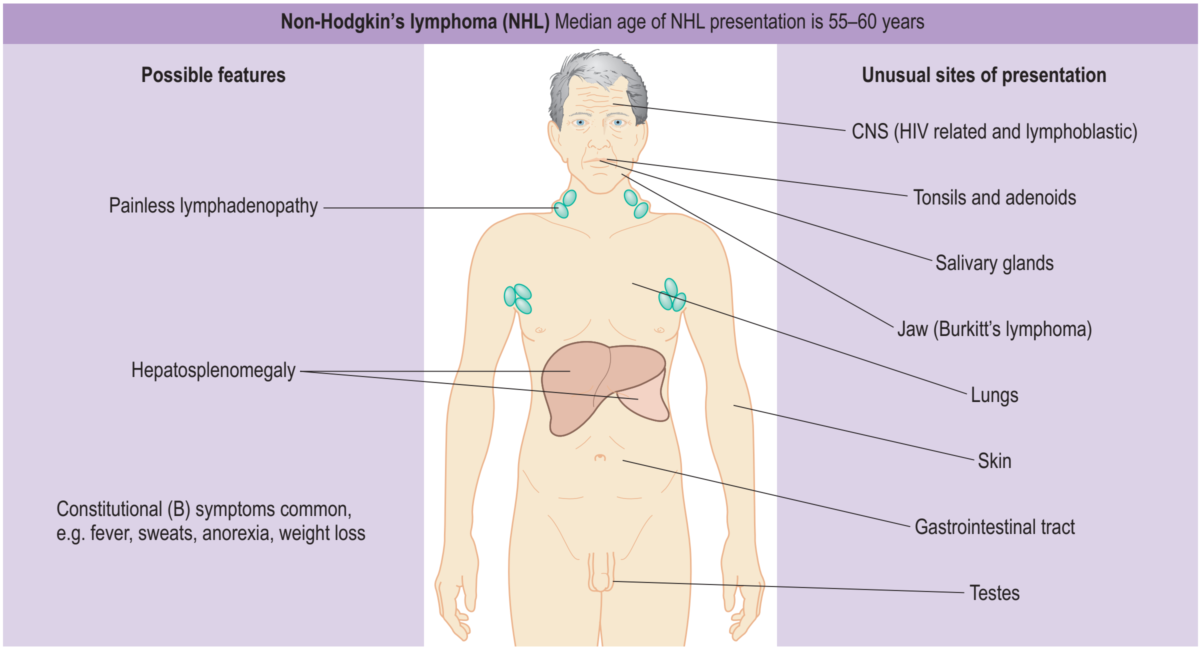

Non-Hodgkin's lymphoma (NHL) Median age of NHL presentation is 55–60 years
Possible features
Painless lymphadenopathy
Hepatosplenomegaly
Constitutional (B) symptoms common, e.g. fever, sweats, anorexia, weight loss
Unusual sites of presentation
CNS (HIV related and lymphoblastic)
Tonsils and adenoids
Salivary glands
Jaw (Burkitt's lymphoma)
Lungs
Skin
Gastrointestinal tract
Testes

Figure 1.70 Non-Hodgkin's lymphoma. CNS, central nervous system; HIV, human immunodeficiency virus.

Interpretation

Confirm the diagnosis

The clinical presentation of lymphoma is very varied:

- Lymphadenopathy is the commonest presentation, especially with lumps in the neck. Obstructive problems represent a later presentation of internal lymph node enlargement, e.g. mediastinum pressure symptoms.
- Organ infiltration is common.
- Systemic symptoms are common.

It is not possible to confirm lymphoma clinically.

Common abnormalities on blood tests are normochromic normocytic anaemia, neutropenia, thrombocytopenia, autoimmune cytopenia, and raised C-reactive protein and erythrocyte sedimentation rate. Hypercalcaemia may be seen in adult T-cell lymphoma / leukaemia and any advanced non-Hodgkin's lymphoma (NHL). Circulating lymphoma cells (large cell, follicular and mantle cell lymphomas) are occasionally detected. Liver and renal dysfunction may reflect organ involvement. Serum or urine paraproteins are more common in indolent lymphomas. Normal immunoglobulins may be reduced.

The diagnostic approach to lymphomas comprises clinical suspicion, imaging and staging and tissue biopsy with standard histology and immunohistochemistry, although molecular tests are not yet as important as in leukaemia. Needle aspirates may exclude carcinoma but are unhelpful in diagnosing lymphoma; the choice is therefore between core biopsy and excision biopsy, the former being less traumatic.

Box 1.52 **Differential diagnosis of lymphadenopathy**

- Infection, e.g. Epstein–Barr virus, cytomegalovirus, toxoplasmosis, tuberculosis, human immunodeficiency virus, brucellosis
- Lymphoproliferative disease, e.g. non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukaemia
- Carcinoma
- Sarcoidosis
- Autoimmune disease

Immunophenotyping on circulating lymphoma cells, aided by cytogenetic studies on tissue specimens obtained, help further diagnosis and classify type. Clonality may be demonstrated by Southern blot or polymerase chain reaction to detect immunoglobulin and T-cell receptor gene rearrangements. Specific translocations occur in certain subtypes, e.g. clonal integration of Epstein–Barr virus.

What to do next – assess other systems

Tell the examiners you would consider the differential diagnosis of lymphadenopathy (Box 1.52).

Consider severity / decompensation / complications

Special problems in lymphoma include pulmonary disease with hilar lymphadenopathy (with a differential diagnosis of tuberculosis), superior vena cava obstruction (SVCO) and cord compression. SVCO is usually due to B-cell NHL. Suspected cord compression requires immediate magnetic resonance imaging; secondary blood vessel thrombosis will cause irreversible problems.

Consider function

Tell the examiners that constitutional symptoms can be very debilitating, as can chemotherapy, and that there is a World Health Organization (WHO) classification for performance status.

Discussion

Is lymphoma common?

The incidence of non-Hodgkin's lymphoma (NHL) is 12 per 100 000, and Hogkin's lymphoma (HL) 2.4 per 100 000. Lymphoma accounts for one-fifth of all cancers in the Western world.

What is NHL?

NHL is a heterogeneous group of malignant diseases characterised by replacement of normal lymphoid structure with diffuse and nodular collections of abnormal lymphocytes.

What causes NHL?

The incidence increases with age, and has increased with human immunodeficiency virus (HIV). Some histological types have geographical associations reflecting environmental factors such as human T-cell lymphotropic virus 1 causing adult T-cell lymphoma/leukaemia, Epstein–Barr virus and Burkitt's lymphoma, and *Helicobacter pylori* and mucosa-associated lymphoid tissue. Immunodeficiency, autoimmune disorders, poisons and some inherited disorders are associated with some lymphomas.

How is NHL classified?

The WHO classification of tumours of haemopoietic and lymphoid tissue in 2008 is not clinically very useful. A classification should contain diseases that are clinically defined, clinically distinctive, non-overlapping and collectively exhaustive; the WHO is exhaustive at 439 pages, but unwieldy. It divides lymphomas into five broad types of mature lymphoid neoplasm with multiple subtypes:

1. B cell
2. T and NK cell
3. Hodgkin
4. Histiocytic and dendritic cell
5. Post-transplantation lymphoproliferative disease.

Each has many subtypes, and some important NHL subtypes are summarised in Table 1.46.

Table 1.46 World Health Organization classification of non-Hodgkin's lymphoma (NHL)

Grade	B-cell NHLs (85%)	T- and NK-cell NHLs (15%)
High grade	DLBCL with subdivisions: • DLBCL GC type / non-GC or ABC-like type • DLBCL associated with chronic inflammation • Lymphomatoid granulomatosis • Primary mediastinal DLBCL • Intravascular DLBCL, • ALK + DLBCL • Plasmablastic DLBCL • DLBCL arising from HHV8 • Castleman's disease, • Primary effusion lymphoma • Unclassifiable DLBCLs with features of Burkitt's lymphoma or Hodgkin's lymphoma Burkitt's lymphoma B lymphoblastic lymphoma / leukaemia	T-lymphoblastic leukaemia / lymphoma Adult T-cell leukaemia / lymphoma T-cell prolymphocytic leukaemia Extranodal NK / T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic T-cell lymphoma Sézary's syndrome Primary cutaneous gamma-delta T-cell lymphoma Peripheral T-cell lymphoma, otherwise unspecified Angio-immunoblastic T-cell lymphoma Anaplastic large-cell lymphoma, ALK positive
Low grade	Small lymphocytic lymphoma (chronic lymphocytic leukaemia) Lymphoplasmacytic lymphoma Splenic marginal zone lymphoma Extranodal marginal zone lymphoma Nodal marginal zone lymphoma Follicular lymphoma Primary cutaneous follicle centre lymphoma Mantle cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma Mycosis fungoides Primary cutaneous CD30-positive T-cell lymphoproliferative disease

ABC, activated B cell; ALK, activin receptor-like kinase; DLBCL, diffuse large B-cell lymphoma; GC, germ cell; HHV, human herpesvirus; NK, natural killer.

Table 1.47 A simplified classification of lymphoid neoplasms

Grade	NHL types	Key points
Low-grade or indolent mature B-cell lymphomas (grow slowly but hard to cure)	Small lymphocytic lymphoma (chronic lymphocytic leukaemia)	(Case 1.46)
	Follicular lymphoma	One-third of all lymphomas Median age 60 years Histologically follicular centre B cells from the germinal centre T(14;18) translocation uniting immunoglobulin heavy chain enhancer region with anti-apoptosis gene Bcl-2 in 80% Lymphadenopathy is predominant presentation (central –abdominal and thoracic, and peripheral)
	Mantle cell lymphoma	More aggressive More common in males Typically presents late middle age with bulky lymphadenopathy and often hepatosplenomegaly and bone marrow suppression
	Hairy cell leukaemia	More common in males Typically younger presentation with palpable splenomegaly May respond well to interferon and purine analogues unlike most lymphomas
	Mucosal-associated lymphoid tissue lymphoma	50% of all gastric lymphomas, classically induced by *Helicobacter pylori* and responsive to its eradication
High grade (grow quickly but easier to cure)	Diffuse large B-cell lymphomas (one-third of all lymphomas)	One-third of all lymphomas Any age, peaking seventh decade Histologically large cells (nucleus typically twice average size) growing in a diffuse (i.e. non-follicular) pattern Arises from antigen-driven B cells which have completed gene rearrangement, CD20 positive Bone marrow involved in 15%
Very high grade (and high risk of central nervous system spread)	Burkitt's lymphoma	Highly aggressive lymphoma of young people
	Lymphoblastic lymphoma	Analogous to acute lymphoblastic leukaemia

NHL, non-Hodgkin's lymphoma.

So non-lymphoma experts get very confused! Indeed, even experts agree that classification is problematic, and a simpler classification of common lymphomas is useful (Table 1.47).

How is lymphoma staged?

HL is staged as lymphocyte predominant, mixed cellularity, nodular sclerosing or lymphocyte deplete. Staging in NHL is less relevant because prognosis in NHL is based largely on histology. Investigations usually include chest X-ray and computed tomography of chest, abdomen and pelvis and biopsy of an appropriate site, and may include bone marrow aspiration and trephine, gastrointestinal investigation, lumbar puncture in high-grade NHL and liver biopsy.

How is NHL treated?

Treatment is based on histological type and prognostic classification, and has advanced markedly recently, with improved supportive care allowing more intensive treatment. It has a much better prognosis in older people than, say, acute myeloid leukaemia. Treatment decisions are based on many factors including age, comorbidity, performance status, disease status and concordance.

Low-grade NHL is usually disseminated at diagnosis, with bone marrow involvement in 75%, and is often incurable, although single-site disease may be cured in 30–50% with field radiotherapy. It has a long natural history, relapsing and remitting, with a median diagnosis of 9 years. Indications for treatment are B symptoms, bone marrow failure, bulky disease or progression.

Diffuse large B-cell lymphoma (DLBCL) in its early stage is treated with combination immunochemotherapy, sometimes with field radiotherapy. Chemotherapy may be with a single alkylating agent (e.g. chlorambucil, cyclophosphamide) or fludaribine with a response rate of 80% for 18–24 months. Interferon-α prolongs remission but does not improve survival. Splenectomy may be curative in splenic lymphoma.

Rituximab is an anti-CD20 monoclonal antibody whose seminal study on follicular lymphoma demonstrated a substantial increase in progression-free and overall survival. Multiple trials confirmed this and rituximab appears highly beneficial in induction and maintenance of relapse in both follicular lymphoma and DLBCL. It is usually combined with chemotherapy regimens, e.g. 'R-CHOP' with cyclophosphamide, doxorubicin, vincristine and prednisolone. Many other antibody therapies have been and are being developed.

Which patients should be considered for central nervous system prophylaxis?

Systemic or intrathecal methotrexate is considered in lymphoblastic, HIV-associated lymphoma, Burkitt's lymphoma or T-cell lymphoma.

Is haemopoietic stem cell transplantation (HSCT) of benefit in NHL?

High-dose chemotherapy and HSCT may benefit younger, high-risk patients with multiple poor prognostic factors. The advantages of allogeneic over autologous HSCT are uncontaminated stem cells and graft versus leukaemia effect.

What prognostic factors are there in NHL?

There are five traditional poor prognostic markers in NHL (Box 1.53).

Gene expression profiling – for example in DLBCL, the germ cell type carries a good prognosis, the activated B-cell (ABC) type a poor prognosis – should prove increasingly useful in determining prognosis and indeed evolving the classification of lymphoma further. The ABC type involves constitutive activation of the NFκB pathway and reflects genes mutated in this pathway and it seems likely that treatments interfering with this pathway will improve prognosis.

The rituximab era may improve prognosis.

What do you know about HL?

This accounts for 30% of all lymphomas. It has a bimodal age distribution. It typically produces peripheral (especially cervical) and mediastinal lymphadenopathy. Histologically the Reed–Sternberg cell is pathognomonic and it may be classified as lymphocyte predominant, mixed cellularity, nodular sclerosing or lymphocyte deplete. Established treatment is with cycles of combination chemotherapy – usually doxorubicin–bleomycin–vinblastine–dacarbazine (ABVD) – followed by involved field radiotherapy, with an excellent outcome (progression-free survival). However, radiation increases the risk of secondary malignancies and cardiac and pulmonary toxicity and negative positron emission tomography computed tomography following early cycles of chemotherapy may identify those who can be cured with chemotherapy alone.

Box 1.53 Poor prognostic markers in non-Hodgkin's lymphoma

- Stage (III or IV)
- Age > 60 years
- Elevated lactate dehydrogenase
- More than one extranodal site involved
- World Health Organization performance status ≥ 2

CASE 1.48 POLYCYSTIC KIDNEY DISEASE

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

The *kidneys are palpable* (confirmed by bimanual palpation and ballottement, but often large enough to cause loin distension) (Fig. 1.71). The *liver may also be enlarged with an irregular surface*, also affected by polycystic disease. There may be a transplanted kidney in the right or left iliac fossa. Bulky polycystic kidneys are usually excised at transplantation.

Interpretation

Confirm the diagnosis

Bilateral flank masses make the diagnosis very likely. Ensure that you can 'get above' the masses. This may be challenging on the right if the liver is also polycystic.

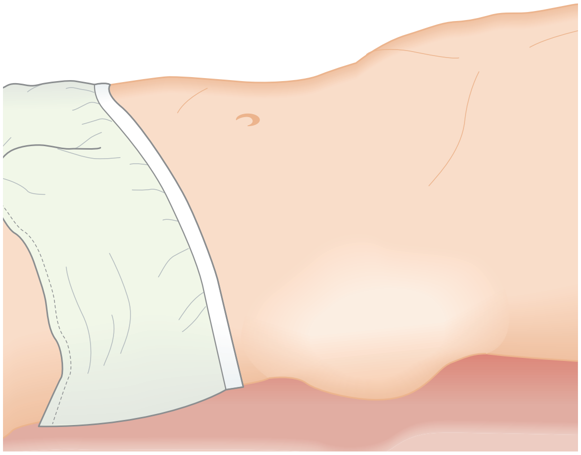


Figure 1.71 Polycystic kidney disease.

Box 1.54 **Extrarenal complications of polycystic kidney disease (PKD)**

- Hepatic, pancreatic or ovarian cysts. These are commonly asymptomatic
- Loin pain or abdominal pain from bleeding into renal or extrarenal cysts / infected cysts
- Mitral valve prolapse
- Anaemia of chronic kidney disease
- Polycythaemia (increased erythropoietin activity)
- Cerebral aneurysms and subarachnoid haemorrhage

What to do next – assess other systems

Tell the examiners that you would like to take the blood pressure, ask about a family history and ask about haematuria.

Consider severity / decompensation / complications

Renal manifestations

Polycystic kidney disease (PKD) may present with haematuria, hypertension, renal failure, large kidneys, loin pain (large kidneys or cyst haemorrhage or nephrolithiasis), or urinary sepsis. Approximately one-third of patients develop chronic kidney disease, one-third develop hypertension without it, and one-third remain asymptomatic through life. Look for evidence of current or previous renal failure (arteriovenous fistula in one or both forearms, scarring at internal jugular or subclavian haemodialysis catheter sites, renal transplantation).

Extrarenal manifestations

Tell the examiners that numerous extrarenal complications may occur (Box 1.54)

Consider function

The flank masses are sometimes uncomfortably bulky. The key is to prevent or delay progression of chronic kidney disease.

Discussion

What do you know about the genetics of polycystic kidney disease (PKD)?

PKD is one of the more common genetic diseases. It may be autosomal dominant (ADPKD) or autosomal recessive (ARPKD, usually presenting in childhood). ADPKD can present at any age, but often in the fourth or fifth decades, and there may be a highly variable phenotype within families. In some families it may become more severe over successive generations (anticipation).

Most patients (85%) with ADPKD have mutations at chromosome 16p (*PKD-1*). *PKD-2* is the next most common genotype. These genes encode polycystin-1 and polycystin-2. *PKD-1* is associated with a more severe phenotype and a higher risk of end-stage renal disease at an earlier age, hypertension and urinary sepsis.

PKD-1 may also be associated with phenotypes of Marfan syndrome, tuberous sclerosis, familial intracranial aneurysm and polycystic liver disease.

The gene mutated in ARPKD encodes fibrocystin, a protein of unknown function.

List some other causes of renal cysts

- Simple cysts, which are extremely common and benign
- Medullary cystic disease, which causes chronic kidney disease
- Acquired cystic disease, which may be found in any scarred kidney
- von Hippel–Lindau syndrome

List some other renal diseases that have a genetic basis

A wide range of cystic, glomerular (e.g. Alport's syndrome, a rare X-linked condition affecting males leading to renal failure; thin basement membrane nephropathy, a relatively common defect in glomerular basement membrane collagen genes causing haematuria with a good prognosis) and tubular transport disorders correlate with pathogenic gene disturbances. In many, multiple different mutations may give rise to the same disease or the same spectrum of disease with slightly differing phenotypic expression. Tubular disorders include:

- Genetic renal glycosuria
- Aminoacidurias, e.g. Hartnup's disease, homocystinuria, cystinuria
- Cytinosis
- Bartter's syndrome
- Gitelman's syndrome
- Nephrogenic diabetes insipidus
- Proximal renal tubule acidosis
- Distal renal tubule acidosis
- Liddle's syndrome
- Glucocorticoid remediable excess
- Apparent mineralocorticoid excess
- Pseudohypoaldosteronism
- Hypophosphataemic rickets
- X-linked hypercalciuric nephrolithiasis (Dent's disease).

Gene mutations responsible for familial renal cancer syndromes, such as tuberous sclerosis complex and von Hippel–Lindau disease, have also been identified.

CASE 1.49 NEPHROTIC SYNDROME

Instruction

Please examine this patient's abdomen and discuss your findings.

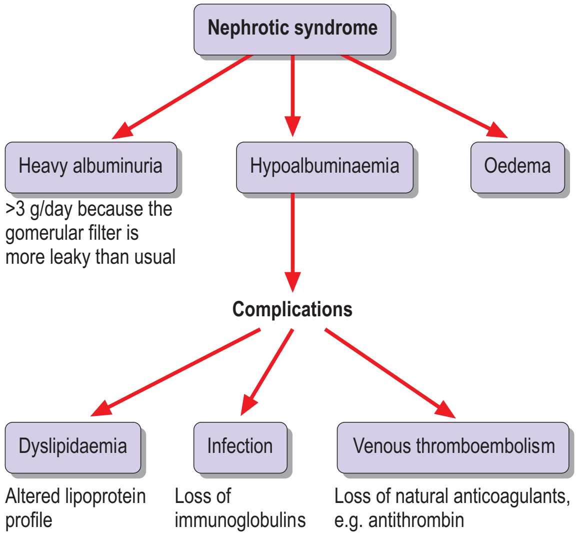

Nephrotic syndrome
Heavy albuminuria
Hypoalbuminaemia
Oedema
>3 g/day because the gomerular filter is more leaky than usual
Complications
Dyslipidaemia
Infection
Venous thromboembolism
Altered lipoprotein profile
Loss of immunoglobulins
Loss of natural anticoagulants, e.g. antithrombin

Figure 1.72 Nephrotic syndrome.

Recognition

There is *fluid overload* as evidenced by *sacral* and *peripheral oedema*. There may be *periorbital* or *facial oedema*. There may be *leuconychia*. Pulmonary oedema is less common.

Interpretation

Confirm the diagnosis

Tell the examiners that you would like to perform urinalysis to check for proteinuria. Nephrotic syndrome is outlined in Figure 1.72.

What to do next – consider causes

The two common primary causes of nephrotic syndrome are minimal change disease and membranous nephropathy. Minimal change disease is usually primary but occasionally associated with Hodgkin's disease. Membranous nephropathy is usually primary but secondary causes include non-Hodgkin's lymphoma, carcinoma, melanoma, gold, penicillamine, diabetes, systemic lupus erythematosus, amyloid, malaria, hepatitis B virus, syphilis and human immunodeficiency virus infection. Tell the examiners that you would take a history and investigate for these.

Consider severity / decompensation / complications

Tell the examiners that you would ask about infection and venous thromboembolism.

Assess function

This depends on the underlying cause.

Box 1.55 **Principles of management of nephrotic syndrome**

- Recognition of histopathological subtype (Case 2.27)
- Identification and specific treatment of any secondary cause
- Salt restriction and diuretics for oedema
- Angiotensin-converting enzyme inhibitors for proteinuria
- Statin therapy for hypercholesterolaemia
- Antithrombotic therapy for prothrombotic tendency (controversial)
- Early recognition and treatment of sepsis (often cellulitis)

Discussion

What are the principles of management of nephrotic syndrome?

These are listed in Box 1.55.

CASE 1.50 RENAL TRANSPLANT

Instruction

Please examine this patient's abdomen and discuss your findings.

Recognition

There is a *palpable renal transplant in the right / left iliac fossa with an overlying scar*. There may be arteriovenous fistulae at the forearms and internal jugular / subclavian scarring from dialysis catheters or scarring from peritoneal dialysis catheters (Fig. 1.73).

Interpretation

Confirm the diagnosis

Refer to Figure 1.73.

What to do next – consider causes / assess other systems

Refer to Figure 1.73. Note that some patients with diabetes receive a kidney and pancreatic transplant.

Consider severity / decompensation / complications

Refer to Figure 1.73 and Table 1.48.

Consider function

Renal transplantation carries the burden of long-term immunosuppressive treatment but allows the possibility of a relatively normal life, unlike long-term dialysis, which is a state of chronic ill-health. Kidney transplant recipients

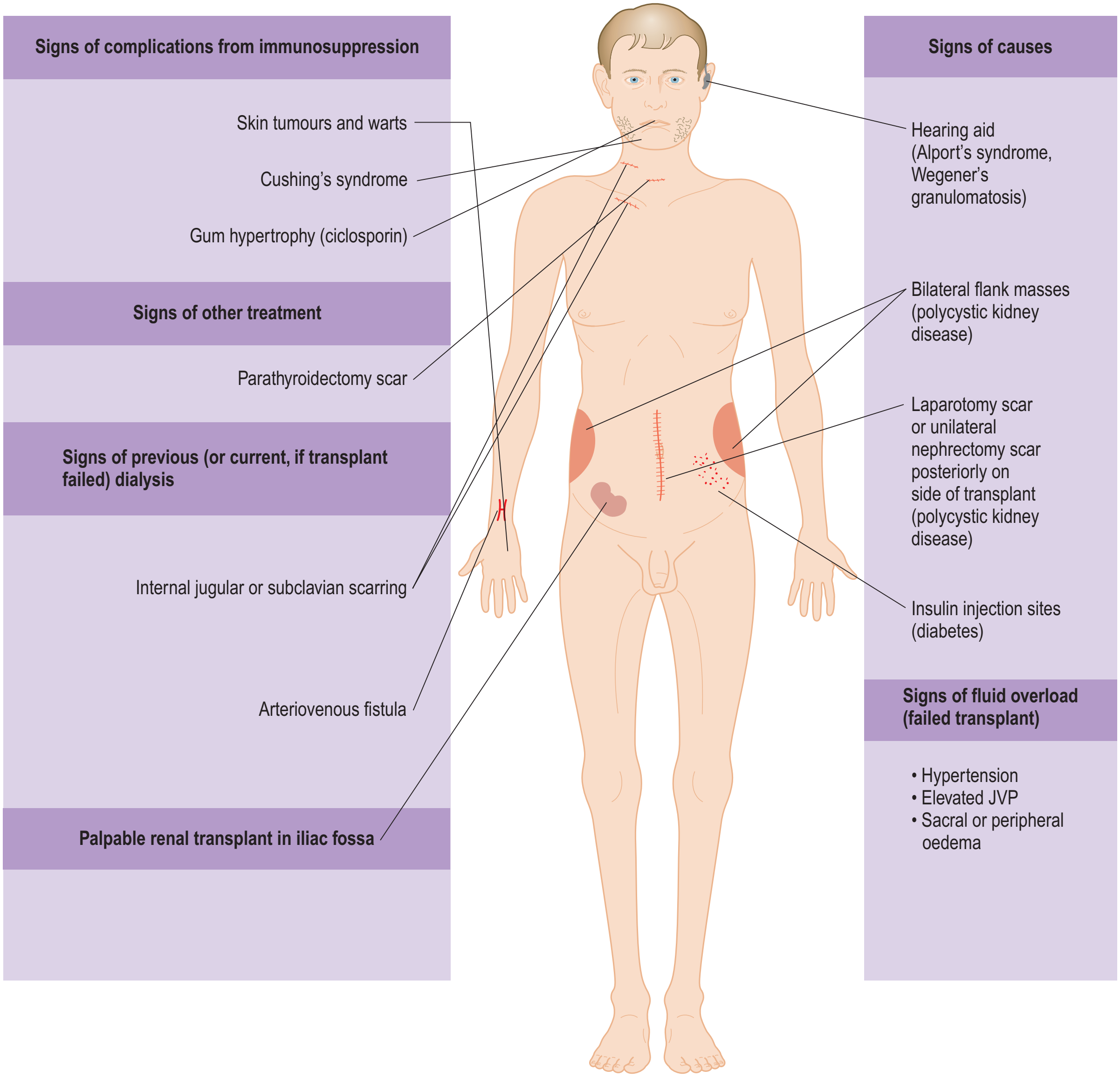

Signs of complications from immunosuppression
Skin tumours and warts
Cushing's syndrome
Gum hypertrophy (ciclosporin)
Signs of other treatment
Parathyroidectomy scar
Signs of previous (or current, if transplant failed) dialysis
Internal jugular or subclavian scarring
Arteriovenous fistula
Palpable renal transplant in iliac fossa
Signs of causes
Hearing aid (Alport's syndrome, Wegener's granulomatosis)
Bilateral flank masses (polycystic kidney disease)
Laparotomy scar or unilateral nephrectomy scar posteriorly on side of transplant (polycystic kidney disease)
Insulin injection sites (diabetes)
Signs of fluid overload (failed transplant)
• Hypertension
• Elevated JVP
• Sacral or peripheral oedema

Figure 1.73 Renal transplantation. JVP, jugular venous pulse.

still exchange one chronic illness for another, however, albeit one likely to change for the better, and must endure a lifetime with increased risk of vascular disease, neoplasia and infection.

Discussion

What types of renal transplant are there?

Donor transplants may be cadaveric or live. Live transplants have a better outcome and are now used predominantly as cadaveric donor organ quality is poor from a progressively older population with comorbidity.

Who may eligible for renal transplantation?

All patients with stage 4 or 5 chronic kidney disease may be considered, but only 30% of patients are fit enough to be listed for transplantation because of excessive comorbidities. Relative contraindications include age, comorbidity, significant untreated coronary artery disease, obesity,

Table 1.48 Complications of renal transplantation

Timing	Complications
Immediate	Hyperacute rejection – may occur within minutes or hours owing to preformed antibodies; graft nephrectomy is necessary Surgical complications – haemorrhage, renal arterial or venous thrombosis, ureteric stenosis, ureteric leak, infection
Early	Acute rejection – occurs in the first few weeks or months owing to host alloreactive T cells which enter the graft Infection, e.g. bacterial, viral (cytomegalovirus very common), fungal (candidiasis), *Pneumocystis* – prophylaxis with ganciclovir if seronegative for cytomegalovirus, co-trimoxazole and antifungal therapy is routine
Late	Surgical complications – renal artery stenosis, ureteral obstruction Chronic rejection – caused partly by alloreactive T cells but immunosuppressive drugs contribute Accelerated vascular disease (reflecting underlying disease and drug therapy) Immunosuppression complications – infection, e.g. polyoma virus; malignancy – warts, skin cancers and lymphoproliferative disorders markedly increased Allograft recurrent disease

Table 1.49 Drugs to prevent rejection

Treatment	How it works	Indication	Side-effects / comment
Corticosteroids	Inhibits nuclear regulatory proteins – powerful anti-inflammatory actions	Maintenance treatment to prevent rejection Treatment of acute rejection	Doses tapered to 5–10 mg daily as maintenance and sometimes stopped High doses to treat acute rejection
Azathioprine	Inhibits purine metabolism and lymphocyte DNA synthesis	Maintenance treatment to prevent rejection	Allopurinol contraindicated with azathioprine as combination may induce aplasia TPMT levels should be checked before starting and dose adjusted accordingly Hepatitis
Mycophenolate mofetil	Inhibits purine metabolism by inhibiting inosine monophosphate dehydrogenase	Maintenance treatment to prevent rejection Post-rejection rescue	More potent than azathioprine Mouth ulcers Diarrhoea Cytopenias
Ciclosporin	Inhibits calcineurin – pivotal molecule in signalling cascade for IL-2 synthesis and hence T-lymphocyte activation and proliferation	Maintenance treatment to prevent rejection	Narrow therapeutic window Nephrotoxic Hypertension Diabetes Hirsutism Gingival hyperplasia
Tacrolimus	Inhibits calcineurin	Maintenance treatment to prevent rejection Rejection rescue	More potent than ciclosporin Diabetes Tremor
Sirolimus	mTOR inhibitor (unlike calcinuerin inhibitors, inhibits response to IL-2 rather than IL-2 synthesis)	Maintenance treatment to prevent rejection	Oedema Proteinuria Hypertriglyceridaemia Anaemia
IL-2 receptor antibodies	Inhibit IL-2, common mediator of Th1 pro-inflammatory pathway	Reduce episodes of acute rejection when added to a ciclosporin regimen	
Anti-T-cell antibodies (OKT3 – monoclonal, ATG – polyclonal)	T-cell inhibitor	Treatment of acute rejection not responding to steroids May be used at induction to prevent rejection	

IL-2, interleukin-2; mTOR, mammalian target of rapamycin. Th1, T-helper type 1; TPMT, thiopurine methyl transferase.

previous malignancy, human immunodeficiency virus infection and chronic hepatitis B or C infection.

What therapeutic strategies are there to prevent rejection?

In both acute and chronic rejection, the initial reaction is between recipient T-cell receptors and donor human leucocyte antigen (HLA) molecules bearing foreign peptides. This leads to a cascade of intracellular and extracellular events, central to which is the production of interleukin-2 (Case 2.46). Recipient–donor matching to reduce rejection involves HLA typing, blood grouping and lymphocytotoxic cross-matching. Renal transplantation is highly immunogenic (unlike cornea, bone and artery grafts), so that immunosuppressive drugs are mandatory for graft survival. Prednisolone, azathioprine and ciclosporin-based triple therapy is a well-established regimen. Newer drugs and regimens aim to reduce rejection and limit side effects (Table 1.49). Immunosuppression has markedly improved 1-year graft survival rates to over 90%. Nevertheless, chronic deterioration of graft function after the first year remains a problem with only minor improvements over the last three decades.

Which diseases recur in a transplanted kidney?

These are listed in Box 1.56.

Box 1.56 **Some diseases that can recur in a transplanted kidney**

- Focal and segmental glomerulosclerosis
- Diabetes (but reasonable prognosis for graft survival)
- Immunoglobulin A nephropathy
- Haemolytic uraemic syndrome / thrombotic thrombocytopenic purpura
- Anti-glomerular basement membrane disease rarely recurs, but linear staining for immunoglobulin G is found in around 50% of biopsies
- Oxalosis

What do you know about post-transplantation lymphoproliferative disease (PTLD)?

PTLD is largely due to the Epstein–Barr virus (EBV), which infects and incorporates itself into the host genome of B lymphocytes. Cytotoxic lymphocytes normally suppress B-lymphocyte polyclonal proliferation but immunosuppressive regimens limit cytotoxic lymphocyte activity and allow B-lymphocyte proliferation. Further unharnessed genetic changes in B lymphocytes may lead to the escape of a malignant monoclonal line. PTLD is less common in patients previously exposed to EBV (immunoglobulin G positive) because some cytotoxicity will already be afforded.

FURTHER READING

Respiratory system

Chronic obstructive pulmonary disease

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Station | 2 |

History-taking skills

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Introduction to history-taking skills

CLINICAL REASONING

Clinical reasoning – what it is

Clinical or diagnostic reasoning is about:

- Identifying relevant clinical information
- Interpreting its meaning
- Establishing a working diagnosis.

The traditional medical history model (Box 2.1) aims, through many questions, to converge gradually towards a diagnosis. Alternative models tend to be based upon, or at least incorporate, communication skills.

Clinical reasoning strategies

Various strategies can be used to get to the diagnosis. Three main ones are hypothetico-deductive reasoning, scheme-inductive reasoning and pattern recognition. Imagine three diagnosticians presented with a four-legged animal. Diagnostician 1 thinks it is a zebra because it looks like one. Diagnostician 2 agrees it is a zebra because it has hooves and stripes and weighs around 300 kg. Diagnostician 3 is from the North Pole and has only ever seen Arctic animals before; he agrees it might be zebra, but also thinks it might be a giraffe because of its hooves or a tiger because of its stripes.

Hypothetico-deductive reasoning

Diagnostician 3 will take some time reaching the diagnosis. He has little knowledge, and would approach the problem by identifying all relevant information, interpreting it, generating hypotheses and testing these. It is the traditional history taking–examination–investigation approach, converging to the diagnosis. It emphasises depth of data collection at the expense of more focused, structured enquiry.

Scheme-inductive reasoning

Diagnostician 2 got to the diagnosis through logic. He has some relevant knowledge and used a scheme or structure that reflected it. It is often an algorithmic approach.

Box 2.1 **The traditional medical history model**

Presenting complaint or complaints

- Identification of the main symptoms – what is wrong and why the patient is in hospital

History of presenting complaint or complaints

- Eliciting symptoms (and consideration of possible causes for each symptom or possible risk factors and complications if a diagnosis is likely)
- Enquiring about investigations and treatments to date

Past medical history

- Eliciting a list of active and past problems

Drug and allergy history

- Drugs past and present

Family history

- Often neglected, but often relevant

Personal and social history

A personal and social history might explore such details as:

- Marital status and health of spouse or partner
- Other family members and relevant medical problems
- Involvement of family and external support services
- Description of accomodation, e.g. flat with lift, house with stairs
- Current and past occupation/s and effects of work on symptoms and effects of symptoms on work
- Support from friends
- Interests and hobbies, including the effects of illness on the quality of these
- Alcohol intake, cigarette smoking and recreational drug use
- Quality of life
- Major effects of illness viewed by patient
- Activities of daily living, e.g. bathing, dressing, shopping, cooking and sleep

Systems review

- Excluding other symptoms through a systems review

Pattern recognition

Diagnostician 1 got to the diagnosis quickly, through experience. She has relevant knowledge. The 'problem' leads to the diagnosis, turning upside down the pyramid that is hypothetico-deductive reasoning. With experience, data are gathered more selectively from the unstructured mass of information. But the evidence is that it takes around 10 years in any field to move from novice to expert, and that experts use pattern recognition successfully most of the time, but when it does not work they must default to a framework.

In PACES, you probably lie somewhere between novice and expert, but closer to expert. What is not in doubt is that you should be thinking about the data you are gathering during history taking, and relating it to the patient's problem.

THE TRADITIONAL MEDICAL HISTORY MODEL

The traditional model

The traditional model is an essential checklist of the content to be covered in a medical history (Box 2.1).

Limitations of the traditional model

The traditional model does not ensure that history taking is effective. Effective history taking is more than asking a checklist of questions, noting responses and formulating a diagnosis at the end.

INCORPORATING THE PATIENT'S PERSPECTIVE – IDEAS, CONCERNS AND EXPECTATIONS

Understanding what patients are thinking

In PACES you have 15 minutes to take a history, witnessed by examiners examining your *history-taking skills* – the *communication skills that make history taking effective*.

Fifteen minutes may seem a short time in which to take a medical history, although general practitioners regularly have less than 10 minutes, relying on focused questions incorporating the patient's perspective. In PACES, as in practice, feeling pressured because you are short of time and trying to extract the 'facts' at all costs from the patient is ultimately less effective than demonstrating these skills. Patients often report things in what seems a chaotic order, dodging from one area of the history to another; candidates might prefer patients to quickly and simply answer questions rather than volunteer extra information. Yet this extra information often contains vital elements of the real problem.

Box 2.2 PACES scenario

You have taken a history from a 52-year-old woman with a painful left calf and mild swelling in the region of the popliteal fossa. You discover that she has had worsening pain for 3 weeks, exacerbated when going up and down stairs, and that sometimes it is so painful it reduces her to tears. She has had to stop work. You discover that she is a nurse on a surgical ward, married, with two children. She has no significant past medical history but 2 months ago was on a long-haul flight, returning from a visit to her sister in Australia. You are told that examination confirms mild swelling in the popliteal fossa and calf tenderness but is otherwise unremarkable.

History taking is a way of guiding what patients say. The best way to understand how history-taking skills can guide patients is to understand what patients are thinking.

Scenario

A PACES scenario is shown in Box 2.2.

The patient's perspective – ideas, concerns and expectations (ICE)

Having taken such a history, you should of course consider the possibility of deep venous thrombosis (DVT). DVT is the most serious of the differential diagnoses, although intuitively you may have some doubts; the duration of symptoms is long and the flight 2 months ago probably irrelevant. Hypothesis testing (pursuing possibilities in turn until they are either excluded or warrant further testing) may also bring a popliteal cyst and muscle strain into the differential diagnosis. You might also wonder whether as a nurse she might be particularly worried about a DVT. She will have seen DVTs on the surgical wards and know them to be dangerous. She might also be aware of the risks of air travel, but unaware that 2 months is a long time to 'harbour' a thrombosis. She is probably apprehensive. Being a patient in hospital or clinic – as a health-care professional to a greater or lesser extent – is being in an alien environment amidst other unwell and sometimes dying people. Many patients have strong preconceptions about doctors and hospitals learned from relatives, friends or the media; doctors seem not to tell patients much, and what they do tell can be difficult to understand; they make mistakes, sometimes with fatal outcomes. This patient might have already decided that she has a blood clot in her leg until proven otherwise. She might know that blood clots can travel to the lung and prove fatal. Much convincing to the contrary might be needed if, for example, her grandmother died from a blood clot (albeit after a fractured hip). She may have seen patients on warfarin, a dangerous drug sometimes taken for life. She might be scared that she has a serious condition requiring dangerous treatment.

These sorts of thoughts going through her mind may be summarised as her ideas (beliefs), concerns and expectations about what her symptoms might represent. She might:

- *believe* she has a blood clot
- be *concerned* about why it has happened and what needs to be done about it
- and *expect* the worst if nothing is done.

A 30-year-old athlete with similar symptoms might believe them to represent a strained muscle, have very few concerns and expect them to go away.

But do not just assume!

Patients do not present just with symptoms, but with thoughts about their symptoms. Some patients volunteer their thoughts. When patients do not volunteer their thoughts, asking is much better than assuming:

What have you been told before/so far about this?
What thoughts have gone through your mind about this?
Are you worried about anything in particular?

Without asking such a question, you will not discover (as the candidate here failed to discover) that the patient was worried she might have multiple sclerosis. Her sister in Australia had presented 2 years earlier with a painful left leg, later diagnosed as multiple sclerosis. She in fact:

- *believed* that she had multiple sclerosis and that it had happened because it ran in her family
- was *concerned* about needing a lumbar puncture
- and *expected* to become wheelchair bound as her sister had.

Failing to establish a patient's thoughts can mean that doctor and patient are looking at the same problem from a different angle, or even two different problems. Discovering a patient's thoughts and any hidden agenda is important. For all sorts of reasons patients do not always report their concerns, and a simple question can confirm:

Your asthma has obviously been troubling you a lot recently. How do you feel we could best help you? By trying to improve the sleepless nights, or something else?

ICE in practice

Overt doctor centredness (pure information gathering) and overt patient centredness (purely addressing the patient's perspective) are extremes of a spectrum. History taking naturally undulates within the spectrum, generally starting with patient-centred open questions:

Your GP says you have had a painful leg. Would you be able to tell me more about that?
Well, yes, I noticed it a week or two ago, but didn't do anything about it.
Why not?
I hoped it would go away. I hoped it wasn't anything serious.
And what has happened since then?

Patient-centred history taking aims to identify a patient's ICE. The following questions are examples of this patient-centred approach:

I expect you've been thinking about this for a while. Are you worried about anything in particular?
I was wondering what thoughts you'd had yourself about this?
What were your own thoughts about this problem?
Have you had any thoughts yourself about what may be causing this?
What did you think might be causing it?
Were you worried it might be due to something in particular?
Some people might have thought it might be due to blood pressure. Did that worry you at all?
When you hear the word …, what does that mean to you?
Tell me what you have heard about …
What types of … have you heard of?
You mentioned a family history of stroke. Is that what really worries you at the moment?
Which part of this bothers you most – is it what the surgeon said or what your wife might think or something else?
What exactly is it about the operation that worries you most?

Patient centredness taken too far can render history taking just as ineffective as pure doctor centredness. History taking should certainly involve guiding a patient back on track if the account starts to wander into areas you feel will not yield useful information; it is perfectly acceptable to say something like:

That is obviously important to you and perhaps we could return to it later, but didn't you say that the main problem you were having was …

How it all affects the patient

Exploring the patient's perspective fully should explore not just ICE, but how the illness or problem(s) affects that patient. This overlaps significantly with the social history. The principle is that it is as important to understand the person who has the disease as it is to understand the disease itself, and it can be helpful to encourage the patient to express their feelings. Opening questions could be:

How is this affecting you at work?
How are you coping at home with this?

HISTORY-TAKING SKILLS – THE COMMUNICATION SKILLS THAT MAKE HISTORY TAKING EFFECTIVE

Communication skills training is now a core component of medical education, and there is good evidence that these skills can be acquired. Important communication skills include:

- Listening skills
- Use of appropriate questions
- 'Eliciting' or facilitating skills
- Recognising and responding to cues
- Use of appropriate language
- Summarising.

Listening skills

As with examining patients and starting with inspection, good history-taking candidates are alert to how patients look, talk and behave. The patient may be relaxed or anxious, waiting for questions, may have already started talking or may pre-empt your opening question:

> I don't know where to start.
> I don't like hospitals.
> I don't know what I'm going to do about my breathing.

The important thing is not to rush in with questions, suppressing information that may provide a valuable insight into what the patient is thinking. Useful opening questions might be:

> What seems to be the problem?
> Your GP says you have had a painful leg. Could you tell me about that?
> Could you tell me why you have come into hospital?

The response might be:

> It's my heart, doctor.
> I just don't seem to have any energy any more.

Again, it is very important to continue listening. Many candidates respond immediately with questions, for example by asking about cardiac symptoms or by assuming the problem to be tiredness and asking about thyroid symptoms. Remember that asking *a direct question usually only gives you the answer to that question!* Careful listening for a minute or two, encouraging the patient to elaborate, will help you form a much more accurate assessment of what the problem is likely to be about:

> I just don't seem to have any energy any more … It all started last October when I began to get short of breath … I'd never been in hospital in my life before that … now I seem to be here every few weeks. I first noticed it when I was out walking my dog. He's always full of energy but I was beginning to find that I couldn't keep up with him any more. I went to see my own doctor because you hear about people suddenly dropping down with heart attacks at my age, don't you? I'd had a few pains in my chest as well. He said that the heart tracing was okay but thought I should have an X-ray – that was when he sent me into hospital.

Your thoughts may now be quite different. Heart failure? Angina? Pulmonary emboli? Chronic obstructive pulmonary disease? Pulmonary fibrosis? The point is that listening, giving a little time for the patient to tell you what has been happening in their words, will give you a clearer idea of the direction you need to take.

Active listening

Active rather than passive listening is showing that you are interested in what the patient is saying. Active listening skills include:

- An attentive manner (it helps to sit forward – not slouching! – and make eye contact)
- Not interrupting (at least, not immediately)
- Encouraging noises, posture and gestures, or the skilful use of silence
- Reflecting back answers to create follow-up questions – *What do you mean by dizzy*?

Use of appropriate questions

Open questions

These are particularly important if you are to avoid jumping to conclusions. They are essential early in the medical interview:

> Can you describe the pain in more detail?
> Can you tell me a little more about that incident?
> And what has been happening since then?
> So you're worried about what this pain says about your health?
> Have you noticed if the pain is brought on by anything in particular?
> May I ask some general questions about your health?
> What has been the result of all of this?

Closed questions

These help to clarify what a patient has said or to obtain factual information that has not been volunteered:

> Have you coughed up any blood?

In general, save closed questions until the patient has had the chance to tell their story. A relevant systems enquiry is, of course, an appropriate series of closed questions.

Eliciting or facilitating skills

Disclosure of relevant medical information and information important to a patient needs to be facilitated. Some patients need little encouragement to talk, and their account should be guided towards what you see as clinically relevant. Some patients are reserved, and need encouragement. Probably the two most important eliciting skills are active listening and the use of appropriate questions. As well as asking open and closed questions, remember that some questions may seem irrelevant to patients and it is important to explain why you are asking them. This may be especially important for sensitive issues:

Some of my patients with emphysema get quite depressed. I often ask patients with emphysema if they have been feeling depressed.

Encouragement

There are many ways of encouraging a patient to continue their account. The simplest yet very effective methods are silence with encouraging facial gestures (smiling and showing concern), nodding, saying *Mmm* or *Yes* and *echoing* what is said:

I have this headache sometimes.
Headache?
Not all the time, but I get it a lot.
Which part of your head gets sore?
This bit. It comes and goes. I wondered if it was serious.
What do you mean by serious?
Well you hear about headaches.
What have you heard?

Interpretation

Reframing or recounting information for patients can help encapsulate information into meaningful 'packages' and show that you understand:

I don't know how best to say it. I'm not depressed exactly.
No, I understand. But I would think you are lonely since your wife died.

Clarification

Sometimes it is necessary to clarify statements that are unclear or need amplification:

Could you explain what you mean by … ?

'Questions in disguise'

Questions that are not actually questions can be very useful for eliciting information.

A statement may be used as question:

It sounds as though that incident alarmed you.

Conjecture may be used as a question:

I was wondering whether …
Sometimes people with headaches worry that it might be something serious …
Sometimes when women have pain like this they worry they might be pregnant …

Sharing an experience or examples can be used as a question:

I had a patient recently who went through a similar …

Legitimising

Legitimising feelings can help a patient to talk openly:

This is clearly worrying you a great deal.
You have a lot to cope with; I think most people would feel the same way.

Recognising and responding to cues

A cue is hard to define, and more easily recognisable. It could be defined as a signpost to an area in the history you might otherwise ignore but which may be very important to the patient. Cues are very common. They are often not consciously presented by patients, but offer an insight into undeclared concerns.

Verbal cues

Examples of verbal cues are:

I hoped it wasn't anything serious.
I don't get paid when I don't work.
It's my chest again.
I just seem to be losing it.
Of course it could just be stress.
Of course it could be my heart.
I'm not worried … after all a lot of those TV programmes just show the worst cases.
It doesn't help that my sisters aren't here.
I hope this won't mean lots of tests. I've got a lot on my plate at the moment.

There may also be cues in the pace, pitch, volume, rhythm or modulation of speech and there may be cues in censored speech – *in what is not said*. Patients frequently hesitate or appear to omit information you intuitively feel should be included:

It's no better (*what's no better?*)
Something will have to be done (*what will have to be done?*)
I'm worried (*about what?*)
I feel worse (*worse than what or when?*)
I'm suffering (*from what?*)
I feel a failure (*why?*)

Sometimes, patients use generalisations to express their concerns:

I don't like hospitals.
No one understands.
I always get headaches.
It never seems to get any better.

Non-verbal cues

Cues may be non-verbal, expressed through body language, facial expression or affect. A patient may look sad or anxious and it might be appropriate to respond:

You look worried about that.

Further, not all cues need an immediate response. Sometimes storing a piece of information and returning to it later is effective:

You mentioned earlier that you hadn't wanted to come into hospital. Was there anything worrying you in particular about hospital?

You will not detect all cues and you do not need to act on all cues that you detect. But examiners will notice if you ignore what seems to be an important cue.

Use of appropriate language

Most importantly, use clear and concise language that you think the patient will understand, and avoid technical terms or jargon that might not be understood, or at least explain any necessary jargon. It can sometimes help to 'match' a patient's verbal and non-verbal behaviour. Patients often speak in visual or auditory terms or in concepts and might say:

> I don't see a way out.
> It sounds like bad news to me.
> It's all a bit much.

Sometimes harnessing the patient's language in this way can enhance rapport and you may find yourself doing it naturally:

> I see what you mean but whilst it may look that way …
> It sounds bad and not what you wanted to hear but …
> I can imagine what you must be going through.

Sometimes, in subtle ways, it is possible to match body language as well as speech. Matching is a two-way process. Speaking loudly and clearly will often encourage a patient to do the same.

Summarising

Summarising periodically

Summarising periodically, as well as at the end of the interview, can be useful in verifying your understanding and in inviting the patient to correct any misinterpretation or add information.

Summarising at the end

Always give your patient a chance to add information or ask questions before concluding. You might ask:

> Is there anything you would like to ask?
> Is there anything else you feel I should know?
> Is there anything important to you that you feel I have left out?

It is good practice to confirm shared understanding:

> May I take a moment to summarise what you've told me so I can check that I've understood everything that is important to you.

Finish by thanking the patient.

THE TRADITIONAL MODEL AND COMMUNICATION SKILLS – PUTTING THESE TOGETHER

Content versus process

The traditional history model describes the *content* of the interview – what to cover. Communication models describe the *process* of the interview – how to do it. Doctors often revert to closed questions and a tightly structured history directed towards gathering medical information. This is understandable because most doctors learned this model, and doctors are seldom observed taking histories but often observed presenting their findings, engendering the erroneous belief that the format for presenting information is the same as that of gathering information. Further, doctors document their findings using the traditional model, augmenting this belief. Because communication skills have previously been taught on courses separate to content skills taught at the bedside, the belief that 'real' doctors take 'histories' and communication skills disregard the clinical history is all too common. Yet the traditional model fails to elicit much of the information needed to understand and manage a patient's problems. Indeed, studies of patient satisfaction, concordance, recall and physiological outcomes validate the need to combine the traditional model with communication skills models. Many communication models exist, such as the Calgary–Cambridge guides. Communication models provide alternative frameworks and lists of skills that are the means by which doctors get through the medical interview, develop rapport, gather information and then discuss their findings and management options with patients.

Content plus process

Because content and process are different frameworks it is easy to see them as alternatives and use only one. Indeed, if not learned and practised together, the tendency is to allow one (usually the traditional model) to inhibit the other. This can lead to many of the common faults in history taking (Box 2.3).

Comprehensive clinical methods that explicitly integrate the traditional model with effective communication skills have been proposed. Table 2.1 is a summary of content working with process that is suitable for Station 2 of PACES.

Box 2.3 **Common faults in history taking**

- Poor introduction
- Inappropriate questions
- Avoiding personal issues
- Lack of warmth or empathy
- Repetition
- Poor clarification
- Poor control
- Poor facilitation of patient disclosure
- Premature or restricted focus

Table 2.1 Putting it together – the traditional history model (content) and communication skills (process)

Content	Process (tasks and communication skills)		
	Structuring the interview Following a logical sequence and keeping on track (doctor's agenda) Summarising periodically Timekeeping	**Introduction** Establishing initial rapport by greeting patient, introducing yourself, and showing respect and interest Identifying the problem(s), best through open questions and listening	**Creating good doctor–patient relationship** Demonstrating appropriate non-verbal behaviour, e.g. sitting at same level as patient, making good eye contact Not letting notekeeping disturb flow Developing rapport by an empathetic and supportive attitude, and legitimising
Gathering information Problem(s) Exploration of problem(s)		**Gathering information** Encouraging the patient's narrative Listening Appropriate use of questions Eliciting or facilitative skills Recognising and responding to cues Appropriate use of language Summarising periodically Exploring ICE and effects on patient	
Medical perspective (disease) Sequence of events Symptom analysis *Patient perspective (illness)* ICE Effects on life			
Background information (context) Past medical history Drug and allergy history Family history Personal and social history Review of systems			
Clinical examination Not possible at this Station in PACES		**Clinical examination** Not possible at this Station in PACES	Continuing to respond to cues Demonstrating confidence Involving the patient, e.g. sharing thoughts, explaining why you are asking a question
Summary – assessment and plan A precise plan may not be possible without examination findings, but it may be possible to say: *From what we have discussed, it is possible that your symptoms could be due to (problem or differential diagnoses). I think we should consider the following test(s) to help confirm this / treatments*		**Explanation and planning** (This is assessed in more detail in Station 4; summarising and agreeing a plan of action is enough for Station 2) Providing right amount and type of information – assessing prior knowledge and extent of patient's wish for information; giving information in manageable chunks; using patient's responses to guide how to proceed Promoting accurate understanding – using appropriate language; organising information (e.g. discrete sections, logical sequence, explicit categorisation: *There are three important points I think we should discuss*); repetition and summarising to reinforce information; visual aids (e.g. drawings); checking understanding and clarifying as necessary Achieving shared understanding and incorporating patient's perspective – relating explanations to previously elicited ICE and encouraging patient contribution and questions Planning by shared decision making – sharing your thought processes and dilemmas and enouraging patient to contribute ideas Inviting questions	
		Closure Forward planning, agreeing with patient next steps and casting a safety net for unexpected outcomes, what to do if plan not working and how and when to seek help Summarising session and plan briefly and final check patient agrees and is comfortable	

ICE, ideas, concerns and expectations.

Cases

Respiratory problems

CASE 2.1 BREATHLESSNESS AND OTHER RESPIRATORY SYMPTOMS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr John Thorn, aged 56 years
> Thank you for seeing this man who has become progressively breathless over six months. Three months ago he developed a lower respiratory tract infection that responded to amoxicillin and doxycycline but he continues to be breathless, particularly on exertion. He smokes and I wonder if he is developing chronic obstructive pulmonary disease. His peak flow is slightly lower than predicted at 420 l/min, although salbutamol and ipratropium inhalers appear to have made little difference. A course of prednisolone did not improve his breathing. Your assessment is appreciated.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr John Thorn is a 56-year-old man who has been troubled by progressive breathlessness on exertion for the past 6 months, with a dry cough. He saw his GP 3 months ago when he developed purulent sputum and although this settled over about 2 weeks with two different courses of antibiotics, his breathlessness and dry cough persisted. He is not breathless at rest, or lying down. He thinks he may have lost a little weight, but has no other notable symptoms. He has smoked 20 cigarettes a day since he was a young man and attributes his symptoms to this. He has no other past medical history of note. He has worked for 30 years as a road-builder. He has never worked in shipyards or building construction and to his knowledge has not been exposed to asbestos. He is not prone to allergies. He has owned the same parrot for the last 8 years and has no other pets. Inhalers have not helped his breathlessness. A course of steroids helped his breathing only marginally. He is worried that if his breathing deteriorates he will no longer be able to visit his brother, who lives in America.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Elicit details of breathlessness.** Find out:

- If it is chronic, and, if so, if it is progressive
- If it came on suddenly or insidiously
- If it is continuous, discrete or with stepwise episodes of worsening (pulmonary emboli; infective exacerbations of chronic obstructive pulmonary disease (COPD))
- If it is present only on exertion, or also at rest, and if there is orthopnoea (left ventricular failure).

■ **Ask about trigger factors.** Ask about exercise, cold, smoking and allergens.

■ **Explore associated symptoms.** Ask about:

- Cough, with sputum (characteristics and volumes – large volumes suggest bronchiectasis) or dry (interstitial lung disease)
- Haemoptysis (lung cancer, pneumonia, pulmonary tuberculosis, bronchiectasis, pulmonary embolus, vasculitis, pulmonary haemorrhage)
- Wheeze (asthma, COPD)
- Symptoms suggesting a cardiac cause (exertional chest pain, orthopnoea, paroxysmal nocturnal dyspnoea, ankle swelling – which may also be due to cor pulmonale)
- Alarm symptoms for malignancy such as weight loss, anorexia, haemoptysis or hoarseness.

Patient perspective

Explore his concerns about the limitations caused by breathlessness, and reassure him that you will do all you can to improve his breathing to enable him to fly.

Past medical history

Ask breathless patients about previous respiratory diseases, such as tuberculosis or asthma, cardiovascular disease or risk factors, and atopy (personal or family history of asthma, eczema or allergic rhinitis).

Drug and allergy history

Many drugs may contribute to dyspnoea, cough or wheeze; specifically ask about non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors.

Family history

Ask about atopy or respiratory disease.

Social history

Ask about:

- Smoking (including passive smoking and pipe smoking – when started / stopped, quantity and pack years)
- Occupations past and present (specifically about the shipyard and building industries for asbestos exposure and road-building for silicosis)
- Travel (atypical pneumonia)
- Pets (cats and dogs commonly trigger asthma, and birds can trigger atypical pneumonia and extrinsic allergic alveolitis).

Consider the effects of symptoms on daily activities and the effects of daily activities on symptoms.

SUMMARY BOX – ASSESSMENT AND PLAN

- Chronic obstructive pulmonary disease (COPD) seems likely in a smoker, but pulmonary fibrosis should always be suspected in a patient with progressive exertional dyspnoea and early on it may be the only feature of disease, with examination and chest X-ray unremarkable; the occupation is important here. Pneumonia that fails to resolve in a smoker should always prompt investigation for possible lung cancer. Exertional dyspnoea also has cardiac causes including ischaemic and valvular heart disease.
- Chest X-ray and spirometry are mandatory initial investigations in suspected COPD or fibrosis.
- Spirometry would confirm obstructive or restrictive lung disease.
- Exertional breathlessness can be the result of cardiac rather than respiratory disease; coronary disease may present as exertional dyspnoea rather than chest pain and if no persuasive respiratory cause is found then exercise tolerance testing is advised.

Discussion

What is silicosis?

Silicosis is a pneumoconiosis caused by inhalation of crystalline silicon dioxide (quartz), which is highly fibrogenic. Many occupations (e.g. stonemasons, road-builders) still involve exposure to quartz dust, which is concentrated in rocks such as granite and sandstone. Particles are engulfed by macrophages and swept to the hilar nodes where inflammation, fibrosis and blockage to lymphatic drainage occur. A similar process can occur in the lungs, provoking small fibrotic nodules. Silicosis does not usually occur with brief exposure; most patients have been exposed for years or decades. With high exposure, small lung nodules can coalesce into large, destructive masses with surrounding bullae. Nodules continue to grow and merge, even after exposure has ceased, causing dyspnoea. Very high exposure occasionally causes an acute inflammatory destructive process with respiratory failure in the absence of nodules. The chest X-ray usually shows 'eggshell' hilar calcification and small (< 5 mm) diffuse nodules. The history, chest X-ray and workplace inspection by an occupational physician usually suffice for diagnosis. Biopsy is seldom necessary, but reveals quartz particles.

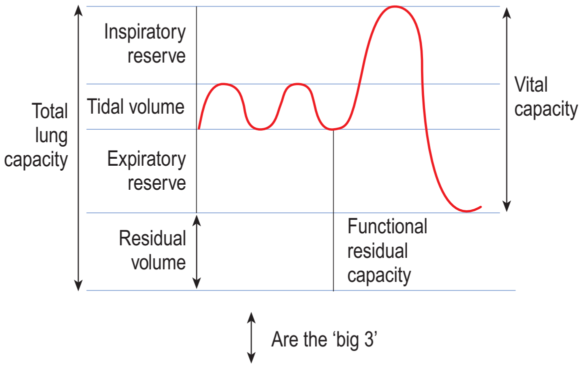


Figure 2.1 Useful lung volumes.

What is meant by the terms total lung capacity (TLC), vital capacity (VC) and residual volume (RV)?

These are shown in Figure 2.1.

- TLC is the total volume of air in the lungs at full inspiration. TLC is limited by the elasticity of the thoracic cage and the fibrous and elastic tissues of the lungs, and by inspiratory muscle strength. TLC varies little with age in healthy people.
- VC is the volume of air expired from full inspiration to full expiration. VC varies widely between healthy people depending upon height, gender and race (3–6 litres) and tends to decrease with age.
- RV is the volume always left in the lung after breathing out the VC. RV is reached when the ribs cannot move closer together. It tends to increase with age and in obstructive lung disease when airways close early in expiration.

Which dynamic volumes are helpful in pulmonary function testing?

The above are static volumes. What we measure mostly in practice are dynamic volumes (volumes which change) because patients are breathing!

- *Forced vital capacity (FVC)* is the forced maximal volume of air expired from full inspiration (TLC) to full expiration (RV), the patient breathing out as hard and for as long as they can. FVC depends

Table 2.2 Obstructive lung disease (OLD) and restrictive lung disease (RLD)

	OLD	**RLD**
Diseases	COPD Asthma	**Intrapulmonary disease:** Interstitial lung disease Lung or lobe resection **Extrapulmonary disease:** Thoracic deformity, pleural disease or inspiratory muscle weaknesss
Static volumes	There is air trapping or hyperinflation TLC preserved or ↑ RV ↑ (early small airway closure and VC ↓) Tidal volume can vary widely	The lungs are small and fibrotic TLC ↓ RV ↓ (alveoli obliterated) Tidal volume often ↓
Dynamic volumes	FEV_1 markedly ↓ (< 80% predicted in COPD) FVC normal or ↓ (because emptying is delayed by airway narrowing and small airways close early in expiration) FEV_1 / FVC ↓ (< 70% diagnostic)	FEV_1 ↓ FVC ↓ (VC is low in RLD, not because of airway problems but because lung volumes are small) FEV_1 / FVC normal or high (> 80–85%)
Expiratory flow rates	↓	Normal
Transfer factor	↓ in COPD, normal in asthma	Normal or ↓

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume over 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

to an extent on the duration of expiration, forced expiratory time varying from normally less than 5 seconds to over 20 seconds in airflow obstruction. Attempts to standardise the FVC using the forced expiratory volume at 6 seconds (FEV_6) have been hindered by the limitations of FEV_6; although FEV_6 (and indeed slow and relaxed VC) seems more reproducible than FVC, it considerably underestimates FVC.

- *Forced expiratory volume over 1 second (FEV_1)* is the amount of air expired over the first second of FVC. FEV_1 is normally > 75–80% of normal VC. FEV_1 is a useful indicator of the severity of obstructive lung disease and a screening test for cardiorespiratory health as it correlates with maximal exercise capacity.

The normal *FEV_1/FVC* ratio is around 70–80%. It is highest in young non-smokers, and declines with age, although < 65% under age 65 is definitely abnormal. Spirometry measures this and differentiates two major groups of lung disease: obstructive or restrictive (Table 2.2).

A mixed obstructive/restrictive pattern occurs when both the FEV_1/FVC and TLC are low, typically in mild COPD with interstitial lung disease.

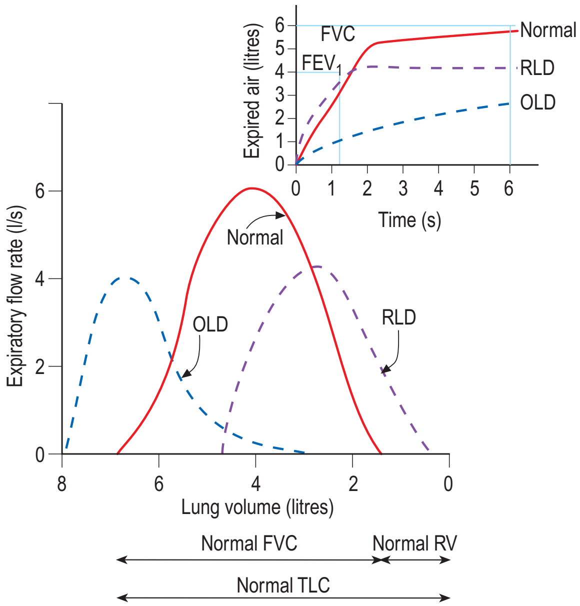


Figure 2.2 Expiratory flow rate plotted against lung volume–normal. FEV_1, forced expiratory volume over 1 second; FVC, forced vital capacity; OLD, obstructive lung disease; RLD, restrictive lung disease; RV, residual volume; TLC, total lung capacity.

What happens to flow rates and flow rate curves in obstructive and restrictive lung diseases?

As well as plotting expiratory flow rate on a volume–time curve, it is possible to plot flow rate (e.g. expiratory flow rate during a FVC manoeuvre) against lung volume (which changes as a person breathes out), as shown in Figure 2.2.

It may seem from Figure 2.2 that the expiratory flow rate in restrictive lung diseases is decreased, but if we correct this for the decreased lung volume in restrictive lung diseases then it is normal or even increased. This is because a fibrotic lung provides more traction than usual on airways, holding them open. Nevertheless, lungs are shrunken and airways are narrowed, increasing their

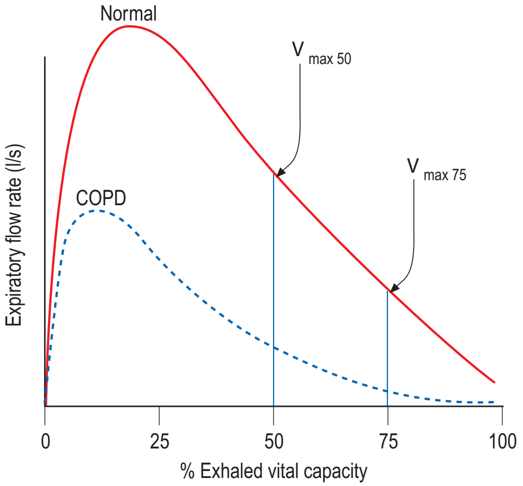


Figure 2.3 Flow rate variation in normal lung and in chronic obstructive pulmonary disease (COPD).

resistance and hence the work of breathing and sensation of inspiratory effort or breathlessness.

In obstructive lung disease, expiratory flow rates are decreased. Although the lungs are hyperinflated, inflammation, oedema and mucus in the smaller airways cause these to close earlier than usual despite normal traction from the lung parenchyma attempting to keep them open.

Note from Figure 2.2 that expiratory flow rates in normal and diseased lungs vary according to lung volume. For example, in normal lungs the maximum flow rate, about 6 litres per second, occurs when about 4 litres of air are left in the lungs. This *peak expiratory flow rate (PEFR)* is normally 300–700 l/min, varying between people as for VC, but reproducible to within 5% for an individual. PEFR tends to be reached shortly after the onset of expiration and subsequently declines as airways narrow and elastic recoil, the effective driving pressure for maximal flow, declines as the lungs get smaller, PEFR reflects airway calibre and respiratory effort, and is most useful for monitoring asthma.

Sometimes, rather than plotting flow rate against volume, flow rate is plotted against percentage VC. This is essentially the same thing, simply plotting flow rate through the various stages of exhaling the VC. For example, when 75% of the VC has been exhaled, the flow rate is called V_{max75}, or forced expiratory flow $(FEF)_{75}$. These measurements are less useful to interpret than the shapes of the curves produced, the former exhibiting large interindividual variation but the latter characteristic in normality and disease and reproducible within individuals.

Note from Figure 2.3 that in healthy individuals the maximal expiratory flow rate (MEFR) decreases steadily throughout forced expiration – as the lungs empty, the airways decrease in size. Note also that the flow rate is low in obstructive lung disease at all stages of exhaling the VC, in other words at all lung volumes. Also note that in obstructive lung disease the curve is scooped out. This dip in MEFR during the middle of forced expiration is one of the earliest signs of small airway damage and is seen in young smokers before clinical features of disease, often with a normal FVC and FEV_1.

What do you understand by compliance and elastic recoil?

Compliance is essentially a measure of the 'give' of the lung when expanding, and elastic recoil is a measure of its ability to shrink to its original size again, like a deflating balloon. Obstructive lung disease lungs are very compliant, but have too little elastic recoil because there is too much airspace and not enough parenchyma. In emphysema elastic recoil is particularly reduced, and FEV_1 is reduced even when the airways are patent. Restrictive lung disease lungs are not very compliant (they are too stiff), having too much recoil, if anything.

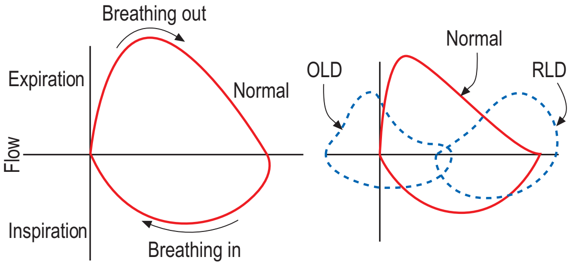
What are flow–volume loops?

Complex mathematics has been applied to produce the shapes of the expiratory flow curves for normal and diseased lungs. Fortunately, physicians do not need to understand the mathematics but need merely to recognise the shapes of certain curves and what they imply. Curves have been created not just for expiration, but also for inspiration. Therefore, as well as flow–volume curves, flow–volume loops (Fig. 2.4) tracking the full inspiration–expiration cycle can be plotted, and these too have characteristic shapes. The expiratory and inspiratory components of the curves are different shapes because of differing forces applied to airways inside and outside the thorax; intrathoracic airways are squeezed during forced expiration, but distended during forced inspiration, whilst extrathoracic airways are 'blown out' on expiration and 'sucked in' on expiration. Flow limitation in expiration is by airway closure; flow limitation in inspiration is by the maximal force and speed of contraction of muscles, and although extrathoracic airways are sucked in, they never become flow limiting.

What do you understand by the term transfer factor and which diseases affect it?

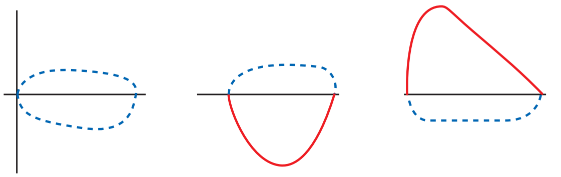
The transfer factor (TLCO) measures total transfer of carbon monoxide across the lung during 10 seconds of breath-holding after full inspiration. It is a measure of alveolar-capillary exchange (surface area and thickness) or effective ventilation/perfusion (V/Q) matching. TLCO is also known as diffusing capacity (DLCO). The KCO, or transfer coefficient, corrects TLCO for lung volume. For example, a TLCO that is half that predicted may occur after a pneumonectomy but the KCO will be normal.

A decreased TLCO (and KCO) occurs in COPD, interstitial lung disease, pulmonary vascular disease (pulmonary emboli, pulmonary hypertension, pulmonary oedema), right-to-left shunts and anaemia. In emphysema, TLCO is misleadingly elevated because CO lingers in the bullae,



Ⓐ **Normal**

Ⓑ **OLD and RLD**



Ⓒ
Fixed upper airway obstruction
e.g.
tracheal stenosis

Ⓓ
Intrathoracic variable obstruction
e.g. tracheomalacia
(can't breathe out)

Ⓔ
Extrathoracic variable obstruction
e.g. bilateral vocal cord palsy (can't breathe in)

Figure 2.4 Flow–volume loops (maximal flow). (A) Normal. Normally, maximal expiratory flow rate (MEFR) decreases during expiration (above), but inspiration is more rapid. Maximal flow rates are much greater than those of tidal breathing (not shown). (B) Obstructive lung disease (OLD) and restrictive lung disease (RLD). In OLD, MEFR decreases during the middle of forced expiration (above) because the small airways collapse just after the onset of forced expiration. For this reason, forced expiration may be less effective than quiet breathing. (C) Fixed upper airway (extrathoracic) obstruction (e.g. tracheal stenosis). Here, MEFR and maximal inspiratory flow rate (MIFR) are reduced equally because of non-compliant or fixed extrathoracic obstruction. (D) Intrathoracic variable obstruction (e.g. tracheobronchial collapse as a consequence of emphysema, tracheomalacia, rare bronchial cartilage disorders). Here, the main problem is with 'breathing out', MEFR being reduced from the start of expiration (MEFR may be constant for the first few hundred millilitres of expiration, after which it behaves like fixed upper airway obstruction). (E) Extrathoracic variable obstruction (e.g. bilateral vocal cord palsy, goitre, acromegaly, laryngeal polyp, episodic in obstructive sleep apnoea). Here, the main problem is with 'breathing in', MIFR being reduced but not MEFR, as extrathoracic airways are narrowed (but remain compliant or flexible) by external compression, luminal obstruction or wall weakness, and flow limited on inspiration but not expiration.

when in fact the obliterated alveoli cause markedly diminished gas exchange.

CO has a high affinity for blood cells, and so transfer is apparently increased in pulmonary haemorrhage, e.g. in the setting of pulmonary vasculitis. TLCO and KCO are also increased in polycythaemia, left-to-right shunts and exercise.

A decreased TLCO and normal KCO is the result of extrapulmonary restriction or 'functional' volume loss, e.g. neuromuscular disease, or volume loss post-pneumonectomy.

What is respiratory failure?

Arterial pCO_2 (p_aCO_2) is normally about 5 kPa (40 mmHg) and is regulated by chemoreceptors. Arterial pO_2 (p_aO_2) is more variable, between 10 and 16 kPa (80–120 mmHg). In type 1 respiratory failure, p_aO_2 is < 8 kPa (60 mmHg) and p_aCO_2 is normal or decreased. Causes include interstitial lung disease, pulmonary vascular disease, asthma and COPD. In type 2 (hypoventilatory) respiratory failure, p_aCO_2 is increased to > 6 kPa (50 mmHg). Causes include COPD, asthma in a tiring patient, and neuromuscular disease.

CASE 2.2 ASTHMA

Candidate information

Role

You are a doctor in the respiratory clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Claire Pickles, aged 30 years

Thank you for seeing this lady with episodes of cough, breathlessness, wheeze and chest 'tightness' for the last few months. Although her symptoms seem to be responding to salbutamol and steroid inhalers I am always a little apprehensive about making a new diagnosis of asthma in adults. I am grateful for your advice as to the likelihood of the diagnosis.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Claire Pickles is a 30-year-old woman who has had episodes of cough, breathlessness, wheeze and chest 'tightness' for the last 4 months, partially responsive to a blue 'treatment' and a brown 'prevention' inhaler. She had eczema as a child but no history of apparent asthma until now and has no other significant past medical history. She moved into a country cottage 6 months ago with her husband and two sons. The cottage is extremely dusty and they are in the process of renovating and rebuilding some of it. Local cats tend to wander in. During house moving she injured her knee and has taken regular ibuprofen for a few months. She cannot understand why she has asthma, as she does not smoke.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

The history should cover similar points to Case 2.1. Asthma not uncommonly starts in adults, and not always with identifiable triggers, and here symptoms are characteristic. She should be asked about diurnal variation of cough (often worse at night and the early hours of the morning, e.g. 02.30–05.00 when endogenous steroids are at their lowest levels), wheeze and shortness of breath. Clinical features that influence the probability of asthma are listed in Box 2.4.

■ **Explore precipitating factors.** These include pollens, dust (house dust mite), animal allergens (cats!), pollens, exercise, viral infection, chemicals (fumes, sprays and perfumes) and irritants (including cigarettes!). Has she, for example, from recently moving house, come into increased contact with more house dust mites? Has she bought a new pet? Has she taken up a new form of exercise? Has she come into contact with any new materials at work? Has she moved in with a smoker?

Patient perspective

Explore her ideas about asthma precipitants.

Past medical history

Ask about previous hospital admissions and particularly whether or not assisted ventilation has ever been needed.

Drug and allergy history

Sometimes symptoms appear or worsen with aspirin, non-steroidal anti-inflammatory drugs, beta blockers or angiotensin-converting enzyme inhibitors. Ask specifically about cumulative oral steroid use with consideration of the need for osteoporosis prophylaxis.

Family history

Ask about a personal or family history of asthma or atopy (eczema, allergic rhinitis).

Social history

Exclusion of smoking is of course essential, as is an occupational history. In addition to a full home and work history (occupational asthma should always be considered in adult-onset asthma, symptoms worse at work), the following three questions should be asked about the last week/month:

1. Have you had difficulty sleeping because of your asthma symptoms (including cough)?
2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
3. Has your asthma interfered with your usual activities (e.g. housework, work, school)?

Box 2.4 **Clinical features that influence the probability of asthma**

Clinical features that increase the probability of asthma

- More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if: symptoms worse at night and in the early morning; symptoms in response to exercise, allergen exposure and cold air; symptoms after taking aspirin or beta blockers
- History of atopic disorder
- Family history of asthma and/or atopic disorder
- Widespread wheeze heard on auscultation
- Otherwise unexplained low forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) rate (historical or serial readings)
- Otherwise unexplained peripheral blood eosinophilia

Clinical features that lower the probability of asthma

- Prominent dizziness, light-headedness, peripheral tingling
- Chronic productive cough in the absence of wheeze or breathlessness
- Repeatedly normal physical examination of chest when symptomatic
- Voice disturbance
- Symptoms with colds only
- Significant smoking history (> 20 pack-years)
- Cardiac disease
- Normal PEF or spirometry when symptomatic (normal spirometry when not symptomatic does not exclude the diagnosis of asthma; repeated measurements of lung function are often more informative than a single assessment)

Other red flags include persistent rather than episodic symptoms, unilateral or fixed wheeze or stridor, cough or breathlessness in the absence of wheeze, other atypical symptoms such as chest pain or weight loss, clinical findings suggesting an alternative cause (e.g. clubbing, crackles, cyanosis).

Discussion

What is asthma?

Asthma is characterised by airway inflammation (often failing to settle between attacks and now appreciated as a core problem in asthma) giving rise to reversible airway narrowing, and airway hyper-responsiveness giving rise to cough, wheeze and dyspnoea. Alveoli and lung parenchyma are spared.

SUMMARY BOX – ASSESSMENT AND PLAN

- She almost certainly has adult-onset asthma, probably atopic asthma.
- Specific immunoglobulin E testing could be undertaken to an array of allergens, or skin prick testing.
- She should be asked to monitor her morning and evening peak flow (demonstrated to her later) in a peak flow diary. A single normal peak flow measurement does not exclude asthma!
- She should be managed according to British Thoracic Society guidelines. She should have a self-management plan, with long-term follow-up by her GP / asthma nurse. An attempt to wean / withdraw her steroid should be made when identifiable triggers are removed.

What do you know about the pathophysiology of asthma?

Asthma and allergic diseases are increasing in prevalence in the Western world, and asthma is predominantly such a disease.

Atopy and allergy

Atopy refers to the predisposition to generate allergic antibodies (i.e. immunoglobulin E; IgE) in response to environmental triggers. The immune system responds to foreign antigens by their being presented to naive T-helper (Th) lymphocytes, which differentiate either to a Th1 response driving intense inflammation or to a Th2 response driving B lymphocytes to switch to IgE production. The optimal scenario is a well-balanced ability to produce Th1 and Th2 responses.

Allergy is associated with a Th2-weighted imbalance.

Atopic predisposition may start in early life, with impaired interferon-γ (IFN-γ) production leading to impaired suppression of Th2 activity involved in IgE-mediated allergy. Healthy neonates have a weak Th2-based immune response that is subsequently suppressed in early life. Exposure to bacteria in early life may increase IFN-γ levels, lending weight to the 'hygiene' hypothesis, which suggests that reduced exposure to bacteria together with antibiotics and modern infant diets result in the persistence of a dominant Th2 pathway. Mycobacterial species are known to stimulate powerful IFN-γ production and research has considered bacterial vaccines to promote switching from Th2 to Th1 pathways.

Allergens in asthma

In asthma, allergens and other unknown antigens are presented by antigen-presenting cells and activate Th2 lymphocytes to produce the Th2 profile of cytokines including interleukins (ILs) 3, 4, 5, 9, 10 and 13. Acutely, these promote histamine release from mast cells. IL-4 and IL-13 have sustained roles that include collaboration with B cells to promote class-switching and release of IgE (which promotes degranulation of mast cell contents – histamine, prostaglandins and leukotrienes), upregulation of adhesion molecules on the capillary endothelium of airway mucosa, and actions on epithelial cells, fibroblasts and airway smooth muscle cells to produce airway narrowing and remodelling. IL-5 promotes eosinophil recruitment to airway mucosa. Eosinophils damage mucosa by protein release, and exacerbate bronchospasm, vascular leakage and oedema (inflammation) by leukotriene release; they also contribute to remodelling through release of fibrogenic mediators such as transforming growth factor-β. It is increasingly appreciated that this intense Th2 eosinophilic activity can lead to persistent inflammation and airway remodelling that may cause accelerated lung function decline.

Are there different types of asthma?

Asthma is a spectrum of disease with aspectrum of triggers.

- Allergic asthma is most common, in which IgE promotes release of mast cell granules immediately and over minutes (e.g. histamine, prostaglandins, leukotrienes), provoking nasal congestion, a runny nose, itchy and watery eyes, wheezing and bronchospasm, followed by, over hours, Th2 cytokine and eosinophil activity. It may be associated with eosinophilia and high blood levels of specific IgE and positive skin prick tests to allergens including grass (particularly perennial rye and timothy grass) and tree pollens, house dust mites, cats, dogs, bird feathers, and sometimes *Aspergillus fumigatus*, the last sometimes being an allergen for asthma without provoking frank allergic bronchopulmonary aspergillosis.
- Food allergens may be non-IgE mediated, and include sulphites and salicylates.
- Occupational asthma is triggered by a wide range of chemicals and foodstuffs.
- Exercise-induced asthma is mostly an expression of poorly controlled asthma.
- Thunderstorm asthma occurs later in the year than many other seasonal triggers and is due to wet conditions affecting activity of the fungus *Alternaria alternatae*; it is increasingly recognised and may result in very severe asthma of rapid onset with numerous presentations to hospital in triggering weather conditions.

How is asthma diagnosed?

Where asthma is highly probable a therapeutic trial is appropriate. Where the diagnosis is not absolutely clear, spirometry should be performed to confirm forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) < 0.7, followed by reversibility testing.

- Asthma is most commonly diagnosed by the peak expiratory flow (PEF) exhibiting > 20% diurnal variation on ≥ 3 days in a week for 2 weeks.
- An increase in $FEV_1 \geq 15\%$ (and 200 ml) after a short-acting β-agonist (e.g. salbutamol 400 μg by

metered dose inhaler (MDI) + spacer or 2.5 mg by nebuliser) or steroids (prednisolone 30 mg/day for 14 days) is also diagnostic.

- A decrease in $FEV_1 \geq 15\%$ after 6 minutes of exercise (running) or a bronchoconstrictor methacholine (or in the future mannitol) challenge may help in difficult cases.

Although percentage changes are quoted, absolute improvements in FEV_1 of > 400 ml with bronchodilator are more specific for asthma; steroid responsiveness is often associated with higher levels of eosinophilic airways inflammation. No significant reversibility suggests chronic obstructive pulmonary disease (COPD).

What do you know about the British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) guidelines for the management of chronic asthma in adults?

Diagnosis may be of high, intermediate or low probability. A treatment trial is indicated for high probability and investigations for alternative causes for low probability. For intermediate probability, especially where FEV_1/FVC is > 0.7, further investigation is preferred alongside a treatment trial for a defined period.

Table 2.3 Stepwise approach to asthma in adults

Step 1: Mild intermittent asthma	Inhaled short-acting β_2-agonist as required
Step 2: Regular prevention therapy	Add inhaled steroid 200–800 μg / day (beclometasone or equivalent)
Step 3: Add-on therapy	Add inhaled long-acting β_2-agonist: if good response continue; if benefit but incomplete control increase inhaled steroid dose to 800 μg; and if no response stop and increase inhaled steroid to 800 μg; if control remains inadequate consider other therapies such as a leukotriene receptor antagonist or SR theophylline
Step 4: Persistent poor control	Consider trials of increasing inhaled steroid to 2000 μg daily or addition of a fourth drug such as a leukotriene receptor antagonist, SR theophylline or a β_2-agonist tablet
Step 5: Continuous or frequent use of oral steroids	Daily steroid tablets in lowest dose possible

Rescue courses of steroid may be used at any time.

Standard therapies

Treatment aims are to control asthma, with control defined as (with minimal side effects):

- No daytime symptoms
- No night-time awakening due to asthma
- No need for rescue medication
- No exacerbations
- No limitations on activity including exercise
- Normal lung function (in practical terms FEV_1 and/or PEF > 80% predicted or best)
- Minimal side effects from medication.

Treatment is stepwise (Table 2.3), starting at the most appropriate step to achieve early control, stepping up as necessary and down when control is good. Patients should be maintained at the lowest possible doses of inhaled steroid, but reductions should be slow, by around 25–50% at 3-monthly intervals.

Omalizumab and emerging therapies

Asthma is often atopic, with aeroallergens interacting with IgE causing release of inflammatory mediators. Evidence is accumulating that the extent of eosinophilic airway inflammation predicts future exacerbations. Single inhaler therapy (e.g. with Symbicort – budesonide/formoterol) appears to improve lung function, reduce exacerbations and produce better symptom control.

Omalizumab is a humanised monoclonal antibody to IgE given subcutaneously, the dose determined by baseline IgE and body weight. It may be used in patients not controlled by optimised standard therapy with positive skin prick tests or specific IgE to perennial aeroallergen(s). The place of other biological agents in asthma is undetermined, and immunosuppressant drugs such as ciclosporin and methotrexate may be considered under specialist supervision.

Increased airway smooth muscle mass may be an important factor in severe or fatal asthma. Bronchial thermoplasty – controlled thermal energy delivered to the airway wall during several bronchoscopy procedures – produces prolonged reduction of smooth muscle mass and can reduce symptoms, reduce use of medication and improve quality of life and lung function.

How would you explain to a patient how to use an MDI?

Instructions are as follows:

- Shake the inhaler and remove the dust cap
- Breathe out gently and fully
- Place the mouthpiece between your teeth and seal your lips around it
- Breathe in steadily, and at the moment you start breathing in ….
- Press the inhaler to release the dose immediately after beginning to breathe in and keep breathing in to full inspiration (until your lungs are full)
- Remove the inhaler from your mouth and hold your breath for 10 seconds or as long as is comfortable
- If a second dose is needed, wait for 30–60 seconds.

Table 2.4 Features of asthma of varying severity

Moderate exacerbation of asthma	Increasing symptoms PEF 50–75% of best or predicted No features of ASA
Acute severe asthma	Any one of: PEF 33–50% of best or predicted Respiratory rate ≥ 25 / min Heart rate ≥ 110 / min Inability to complete sentences in one breath
Life-threatening asthma	PEF < 33% of best or predicted $SpO_2 < 92\%$ Respiratory failure on arterial blood gases – $p_aO_2 < 8$ kPa (rising p_aCO_2 a sign of near-fatal asthma) Silent chest Cyanosis Poor respiratory effort Arrhythmia Exhaustion, altered conscious level

ASA, acute severe asthma; PEF, peak expiratory flow.

How should patients with asthma be monitored?

It is unclear how best to monitor patients, although regular follow-up by doctors and nurses trained in asthma management may be beneficial, but asthma control can be assessed by well-validated questions, such as those in the asthma control test with a specific scoring system:

How much of the time did your asthma keep you from getting as much done at work, school, or home?
How often have you had shortness of breath?
How often did your asthma symptoms wake you up at night or earlier than usual in the morning?
How often have you used your rescue inhaler or nebulised drug?
How would you rate your asthma control?

How would you recognise acute severe asthma (ASA) and life-threatening asthma?

Features of moderate exacerbations, ASA and life-threatening asthma are listed in Table 2.4.

How would you manage acute asthma?

High-flow oxygen and β_2-agonist bronchodilators by nebuliser are administered to all patients. Nebulised ipratropium bromide (0.5 mg 4- to 6-hourly) may be added to the β_2-agonist for ASA or life-threatening asthma or when initial response to β_2-agonists is poor. Systemic steroid (e.g. prednisolone 40–50 mg daily) is administered to all patients. A single dose of intravenous magnesium sulphate (1.2–2 g by 20-minute infusion) is considered in ASA without a good initial response or in life-threatening asthma. Referral to the ITU should be made in those circumstances outlined in Box 2.5.

Box 2.5 **Indications for referral to ITU in acute asthma**

This is indicated if ventilatory support is needed or if acute severe asthma or life-threatening asthma is failing to respond, as evidenced by any of the following:

- Deteriorating peak expiratory flow
- Persistent or worsening hypoxia
- Hypercapnia, acidosis
- Exhaustion
- Feeble respiration
- Drowsiness
- Confusion
- Coma
- Respiratory arrest

Box 2.6 **Criteria for safe discharge following acute severe asthma**

- Identification and modification of trigger factors achieved where possible
- Patient on discharge medication for at least 24 hours
- Peak expiratory flow (PEF) > 75% of predicted or best and preferably PEF diurnal variability < 25%
- Patient on steroids in addition to bronchodilators
- Patient has individualised management plan, and, where possible, is able to self-monitor their PEF
- GP and specialist follow-up arranged with good communication between all parties

Does asthma management differ in pregnancy?

The β_2-agonists, steroids and theophyllines are each used as normal, but leukotriene receptor antagonists have not been adequately researched. Poorly controlled asthma is worse for the baby than any risk from oral steroids. ASA management is unchanged.

When would you consider it safe to discharge a patient from hospital after ASA?

Discharge is appropriate under those criteria listed in Box 2.6.

What might you consider when a patient has chronic asthma that is difficult to control?

There is no clear definition of difficult asthma but it is reasonable to consider it when there are persistent symptoms and frequent exacerbations despite being treated at steps 4 or 5 of the guidelines. Patients typically need high-dose inhaled steroids (≥ 800 μg beclometasone equivalent), a long-acting β_2-agonist, plus add-on treatment. Several considerations are needed with difficult asthma.

Alternative diagnosis

These include cardiac diseases such as heart failure and other lung diseases, including the systemic vasculitis Churg–Strauss syndrome, the severity of which may be masked by steroids. Investigations that may be needed in patients with difficult asthma may include:

- *Blood tests:* Eosinophil count (and induced sputum eosinophil count), total serum IgE and allergen skin prick testing (or radioallergosorbent test) especially to *Aspergillus*, *Aspergillus* serology, antineutrophil cytoplasmic antibody, α_1-antitrypsin
- *Pulmonary function:* Spirometry, flow–volume loops, bronchodilator reversibility with 400 µg of inhaled salbutamol if airflow obstruction present, and if airflow obstruction absent consideration of exercise testing or bronchial challenge testing using inhaled methacholine or mannitol, and exhaled nitric oxide (raised in eosinophilic airway inflammation)
- *Radiography:* Chest radiography, high-resolution computed tomography of the thorax (for bronchiectasis or interstitial lung disease), computed tomography of sinuses (for sinus disease after nasal endoscopy or a trial of nasal steroids)
- *Other tests (as clinically indicated):* Nasal endoscopy (for polyps and rhinosinusitis), bronchoscopy (for tumours or foreign bodies), laryngoscopy during symptomatic episodes (for vocal cord dysfunction), echocardiogram (where wheeze may be 'cardiac asthma').

Coexisting conditions

Asthma often occurs alongside other conditions, and bronchiectasis, gastro-oesophageal reflux disease, rhinosinusitis and psychological disorders are more common in people with frequent versus infrequent severe exacerbations of asthma. Vocal cord dysfunction (paradoxical adduction during inspiration) is a disorder that can mimic or coexist with asthma.

Persistence of aggravating factors

These include:

- Psychological factors and stress
- Upper airway disease (asthma and allergic rhinitis are a continuation of the same inflammatory process)
- Allergy
- Gastro-oesophageal reflux disease
- Drug side effects
- Occupational exposure
- Smoking
- Obesity.

Concordance

Reasons for this include treatment considered unnecessary or ineffective, poor understanding of the regimen and poor inhaler technique

Is asthma preventable?

Breastfeeding, parental non-smoking and weight reduction may be important in primary prevention. Nutritional intake in pregnancy, dietary manipulation, the role of microbiological exposure and immunotherapy are all being studied. Not smoking is helpful in secondary prevention, and allergen or air pollution avoidance seems logical and may be useful where dust mites are a cause, although studies on pet removal are not robust; there may be a role for immunotherapy.

Are inhaled medications dangerous?

Any inhaled substance (not necessarily the drug itself) will cause bronchospasm in some people; β-agonists can cause severe exacerbations and deaths in asthma, but not in COPD. Anticholinergics are generally very safe in COPD with small concern about vascular events. Inhaled corticosteroid predisposes to pneumonia in COPD but not asthma, and benefits outweigh risks.

Abdominal problems

CASE 2.3 DYSPEPSIA AND UPPER GASTROINTESTINAL BLEEDING

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Elizabeth Richards, aged 67 years

Thank you for seeing this lady who is anaemic with a haemoglobin of 10 g/dl. She has lost 7 kg in weight over a few months. Four years ago she had grade 3 oesophagitis diagnosed on biopsy and has been on omeprazole 40 mg daily since. Her routine biochemistry is normal. Her ferritin is borderline low. I would value your assessment and advice on further investigation.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be

Box 2.7 **The causes of dyspepsia**

Gastro-oesophageal reflux disease (GORD) with or without oesophagitis

Heartburn is the primary symptom of GORD, and other common symptoms are regurgitation, belching, epigastric pain, chest pain, dysphagia and acid brash. Symptoms are typically after meals, on bending or lying flat. Less common symptoms include nausea, odonyphagia (painful swallowing), dysphonia and hoarseness (posterior pharyngitis, contact ulceration or subglottic stenosis), globus hystericus, recurrent aspiration, nocturnal and post-prandial cough, and chest pain mimicking angina. Symptoms of GORD, however, can be highly variable.

Peptic ulcer disease

Symptoms include epigastric pain and a history of haematemesis or melaena. The common causes are *Helicobacter pylori* and non-steroidal anti-inflammatory drugs.

Upper gastrointestinal malignancy

This refers to malignancy of the oesophagus and stomach (cancer, mucosa associated lymphoid tissue lymphoma). Ask about alarm features:

- **A** anaemia
- **L** loss of weight (a worry, prompting check of inflammatory markers) or anorexia
- **A** abdominal mass
- **R** recent onset of progressive symptoms
- **M** melaena or haematemesis
- **D** dysphagia or vomiting

Other high-risk factors for cancer in dyspepsia include a family history of upper gastrointestinal malignancy, previous gastric ulceration, previous gastric surgery, known intestinal metaplasia or atrophic gastritis and known Barrett's oesophagus.

'Functional' dyspepsia

This remains essentially a diagnosis of exclusion, and its causes are uncertain; although around half may test positive for *H. pylori* this approximates the prevalence in asymptomatic individuals. It is the most common cause of dyspeptic symptoms, accounting for about 50% of cases. Of the remainder, around 20% have endoscopy-negative reflux disease, 20% have oesophagitis, 10% have peptic ulcer disease, 2% have Barrett's oesophagus, and 1% have malignancy. Therefore, around two-thirds of patients with dyspeptic symptoms have no structural lesions.

prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Elizabeth Richards is a 67-year-old woman who is anaemic. She has lost around 1 stone in weight over the last few months and feels that her abdomen is getting 'fuller'. She has a little discomfort in her chest after eating but no vomiting or alteration in bowel habit. She has type 2 diabetes, which is controlled by diet. Four years ago she had heartburn and endoscopy revealed moderately severe oesophagitis and she has taken omeprazole since. She takes no other medications, and in particular has not taken non-steroidal anti-inflammatory drugs (NSAIDs). She does not drink alcohol or smoke. She has a family history of breast cancer, her mother and sister both being affected. She feels well, apart from the above, and wonders why she cannot simply take iron tablets to correct the anaemia. She will ask the doctor why further tests are necessary and has not considered malignancy as a possibility needing exclusion.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Consider the causes of dyspepsia.** Around 25–40% of adults in the general population have dyspepsia. Dyspepsia refers to a group of symptoms arising from the upper gastrointestinal tract including epigastric or upper abdominal discomfort, post-prandial fullness, early satiety, heartburn, and regurgitation. Many definitions exist. The National Institute for Health and Clinical Excellence considers dyspepsia as any chronic and recurrent symptoms referable to the upper gastrointestinal tract. Patients with heartburn and regurgitation only should be considered to have gastro-oesophageal reflux disease. The symptoms may indicate one of four possibilities (Box 2.7).

■ **Consider the differential diagnoses of dyspepsia.** A cardiac history is essential because cardiac pain and dyspepsia can be difficult to distinguish. Other causes of upper abdominal pain include aerophagy, biliary disease, abdominal wall pain, chronic pancreatitis, mesenteric ischaemia, diabetes and hypercalcaemia. Individual dyspeptic symptoms or subgroups of symptoms poorly predict the presence of underlying organic lesions, although the presence of predominant heartburn and regurgitation may help predict underlying gastro-oesophageal reflux disease.

Patient perspective

Explore her ideas and expectations about simply treating anaemia with iron and explain the reasons for wanting to investigate further.

Past medical history

The history of oesophagitis is important, even though she has taken a proton pump inhibitor (PPI), because it can transform to oesophageal malignancy.

Drug and allergy history

Ask specifically about NSAIDs or corticosteroids (often for chronic inflammatory conditions such as asthma, inflammatory bowel disease and connective tissue disease). Aspirin, antibiotics, calcium antagonists, theophyllines and bisphosphonates also provoke dyspepsia.

Family history

The family history of breast cancer may be relevant because it may link with ovarian cancer. The latter must be in the differential diagnosis as a cause of weight loss, abdominal fullness and unexplained anaemia that may not be iron deficient.

Social history

Ask about alcohol and smoking, both risk factors for peptic ulceration.

SUMMARY BOX – ASSESSMENT AND PLAN

- Recurrence of oesophagitis or oesophageal malignancy must be excluded. Other possibilities include malignancy elsewhere including colorectal cancer and ovarian cancer.
- A full examination including a rectal examination would be mandatory.
- Initial blood tests should include a full blood count, haematinics, inflammatory markers, renal and liver function, calcium and thyroid function.
- An urgent oesophagogastroduodenoscopy and possible imaging of abdomen and pelvis would seem sensible initial investigations.

Discussion

What do you know about the types of gastro-oesophageal reflux disease (GORD)?

The Montreal classification defines gastro-oesophageal reflux disease (GORD) as 'a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications'. It is potentially, although rarely, serious. A clear history of heartburn (a rising feeling from the stomach to the neck) is unlikely to be caused by anything else and quality of life is affected in proportion to the frequency and severity of this, irrespective of the presence or severity of oesophagitis. The acid component of the gastric refluxate is responsible for most of the symptoms and pathology associated with GORD, although other components, such as bile, may also contribute (known as non-acid reflux). The prevalence of reflux symptoms is around 44% with 24% of individuals experiencing symptoms for 2 days or more per week.

Non-erosive reflux disease (NERD)

Nearly 70% of patients with heartburn do not have evidence of erosive changes on endoscopy. Of these, a proportion has increased acid reflux on 24-hour pH monitoring and is classified as having NERD.

Functional heartburn

A proportion of patients describe typical reflux symptoms without evidence of reflux. It is likely that acid exposure is not the major cause of symptoms and the pathophysiology remains obscure.

Reflux oesophagitis

Reflux oesophagitis implies reflux of gastric contents causing mucosal damage (inflammation or ulceration) of the oesophagus, and may be symptomatic or asymptomatic. Attempts have been made to classify the extent of damage, and the Los Angeles classification is now commonly used: A – mucosal breaks of < 5 mm not extending between folds; B – mucosal breaks of > 5 mm not extending between folds; C – mucosal breaks extending between at least 2 folds; D – mucosal breaks extending between > 2 folds involving > 75% of the circumference.

What is the pathophysiology of GORD?

GORD is associated with transient lower oesophageal sphincter (LOS) relaxation unrelated to swallowing or to failed swallows – those not followed by normal peristalsis. The LOS is a 3–4 cm region of smooth muscle in the distal oesophagus and externally, the crural diaphragmatic striated muscle, the latter being incompetent in a hiatus hernia. Other factors contributing to the magnitude of reflux include oesophageal clearance and neutralisation mechanisms. Relaxation of the LOS and crura are normal physiological processes during swallowing and gas venting. Relaxations not initiated by a swallow are known as transient lower oesophageal sphincter relaxations (TLOSRs). TLOSRs probably account for 90% of reflux episodes. The TLOSR reflex is initiated by tension receptors in the stomach and mediated by a vagovagal pathway via the brainstem; these responses are inhibited by gamma-aminobutyric acid-B (GABA-B) receptor agonists, a future potential therapeutic target. Hiatus hernias appear to increase the magnitude of reflux during TLOSRs. TLOSRs appear to be less significant in more severe reflux oesophagitis. Factors which relax the LOS, such as caffeine, fat, smoking, drugs (calcium channel antagonists and nitrates) and gastric distension, increase the likelihood of reflux. The association of increased body mass index and GORD remains unclear.

What are the complications of GORD?

GORD can lead to the complications listed in Box 2.8.

The prevalences of oesophagitis and Barrett's oesophagus are 12% and 1.3%, respectively, irrespective of symptoms. Traditionally, oesophagitis was seen as a continuous spectrum of disease, with endoscopy-negative symptoms labelled as mild and Barrett's oesophagus labelled as very severe. However, progression from normal to erosive oesophagitis to Barrett's oesophagus is seldom seen and symptoms are tending to replace mucosal findings in determining severity.

Box 2.8 **Complications of gastro-oesophageal reflux disease**

- Oesophagitis (various grades, if severe leading to scarring and strictures)
- Barrett's oesophagus (upward propagation of columnar epithelium, replacing squamous epithelium)
- Oesophageal carcinoma (the majority are squamous, but adenocarcinoma is a complication of Barrett's oesophagus)

What is the relationship between a hiatus hernia and GORD?

A hiatus hernia does not diagnose GORD. The majority of hiatus hernias are asymptomatic (rarely, a hiatus hernia may undergo torsion to cause acute pain and vomiting) although 90% of patients with severe oesophagitis will have a hiatus hernia.

How may GORD be investigated?

Most patients with typical symptoms of GORD do not require investigation and will respond to a trial of PPI. High-dose PPI (40 mg omeprazole twice daily for 1 week) has a sensitivity of 80% as a diagnostic test for GORD.

Oesophagogastroduodenoscopy (OGD)

Patients of any age presenting with reflux symptoms and alarm symptoms should have an urgent OGD. OGD should also be performed before oesophageal pH studies. Otherwise OGD in the assessment of heartburn is not indicated. Further, a negative OGD does not exclude NERD. Screening for Barrett's oesophagus in patients of any age with a history of chronic heartburn cannot be recommended as the absolute risk of adenocarcinoma is less than 1 : 1000 and 40% of patients who develop adenocarcinoma in association with Barrett's oesophagus do not have a history of heartburn.

Oesophageal ambulatory pH studies

Acid exposure of the distal oesophagus can be measured either by placing a naso-oesophageal probe 5 cm above the LOS or by placing a wireless capsule probe endoscopically. Measurements of pH can be taken for 24 or 48 hours. PPIs or histamine receptor antagonists (H2A) should be stopped 1 week before the procedure. Acid exposure above normal ranges is considered pathological. The indications for pH studies are:

- Patients with typical symptoms of GORD who fail to respond to a trial of PPIs (it is alternatively reasonable to escalate PPI dose in these patients)
- Patients with typical symptoms of GORD without oesophagitis or an adequate response to PPIs who are contemplating anti-reflux surgery
- Patients with persistent GORD symptoms after anti-reflux surgery.

Oesophageal manometry

Oesophageal manometry seldom influences GORD management It may be useful where oesophageal motility abnormalities are suspected, such as achalasia.

Multichannel intraluminal impedance

This measures changes in electrical resistance within the oesophagus, which can imply the direction and duration of refluxate. It may be useful in the investigation of PPI-resistant reflux symptoms although its role is not well defined.

Why is Barrett's oesophagus important and how is it managed?

It can be a precursor to adenocarcinoma of the oesophagus (relative risk around 80-fold). Cancer is heralded by high-grade dysplasia and is more likely with a long segment (> 7 cm) of Barrett's oesophagus. Endoscopic surveillance is appropriate every 1–2 years if there is no significant dysplasia. There is no evidence that PPIs or anti-reflux surgery lead to regression of Barrett's oesophagus.

Other than GORD, what other causes of oesophageal pain are there?

GORD is the most common cause, but motility disturbances, increased or decreased – as in achalasia – can occur, as can hypersensitivity and often an overlap of these problems. Oesophageal spasm, relieved with nitrates, is very rare.

List some causes of duodenal and gastric ulceration

These are listed in Table 2.5.

What do you know about *Helicobacter pylori*?

Helicobacter pylori is a Gram-negative bacillus that colonises only the mucus layer of the human stomach. It is one of the most common human infections; about half of the world's population carries this organism, although the prevalence varies widely, with more than 80% of adults being infected in Japan and South America compared with around 40% in the UK. Most infected people (> 70%) are asymptomatic. However, there is strong evidence that *H. pylori* has an important causative role in > 90% of duodenal ulcers and a role in benign gastric ulcers that are not attributable to NSAIDs. There is evidence of a causative role in gastric cancer and gastric-mucosa-associated lymphoid tissue lymphoma. It may have a role in functional (non-ulcer) dyspepsia. Although *H. pylori* initially causes inflammatory gastritis, the immunological response is not sufficient to clear it and it becomes chronic. Polyclonal strains are common. It is, however, decreasing in prevalence.

Table 2.5 Causes of duodenal and gastric ulceration

Duodenal ulceration	Gastric ulceration
Helicobacter pylori infection (> 90%) NSAIDs Zollinger–Ellison syndrome Hypercalcaemia Granulomatous disease (Crohn's disease, sarcoidosis, Wegener's granulomatosis) Neoplasia (carcinoma, lymphoma, leiomyoma, leiomyosarcoma) Infection (tuberculosis, syphilis, herpes simplex, cytomegalovirus, *Candida*) Ectopic pancreatic tissue	*Helicobacter pylori* infection (non-atrophic gastritis, although the latter is usually autoimmune) NSAIDs Neoplasia (carcinoma, lymphoma, leiomyosarcoma) Granulomatous disease (Crohn's disease, sarcoidosis, Wegener's granulomatosis) Infection (tuberculosis, syphilis, herpes simplex, cytomegalovirus, *Candida*) Radiotherapy

NSAID, non-steroidal anti-inflammatory drug.

What do you know about the pathophysiology of peptic ulceration and gastric cancer, and their links with *H. pylori*?

Normal gastric secretion

The stomach comprises a proximal fundus, a body and a distal antrum. Parietal (oxyntic) cells in the body and fundus produce hydrochloric acid and intrinsic factor. Chief (peptic) cells secrete pepsinogen, a pepsin precursor. Stimulation of these and other gastric secretions has neuronal (vagal), hormonal (gastrin) and histamine (stimulated by gastrin) inputs. Inhibition of secretion is mediated by sympathetic nerve activity, low pH and negative feedback from small bowel enzymes. Gastrin is produced from G cells in the antrum. Its secretion is stimulated by food, distension, vagal input and high pH. Gastrin promotes acid, intrinsic factor and pepsin secretion (the H_2 receptor being the final common pathway), gastric emptying, pancreatic bicarbonate release and secretin release. Somatostatin in the antrum inhibits gastrin release. The pieces of information important here to the development of peptic ulceration and gastric cancer are that:

- Acid is produced from the body and fundus of the stomach
- Gastrin, which stimulates acid, is produced in the antrum
- Somatostatin, which inhibits gastrin, is also produced in the antrum.

How peptic ulceration develops

Patients with duodenal ulcers have excessive numbers of parietal cells with acid hypersecretion. That acid hypersecretion is virtually always due to *H. pylori* is evidenced by the fact that secretion returns to normal when *H. pylori* is eradicated. A predominantly antral gastritis due to *H. pylori* occurs in *H. pylori*-provoked duodenal ulcers (the vast majority are *H. pylori* provoked). This tends to cause suppression of somatostatin cells and a consequent increase in gastrin release from G cells leading to acid hypersecretion. Further, areas of gastric metaplasia in the duodenum can be colonised by *H. pylori*, causing duodenitis; gastric metaplasia increases with the amount of acid entering the duodenum and tends to be lowest in pernicious anaemia (in which acid-producing areas are destroyed) and highest in patients with gastrin-secreting tumours (Zollinger–Ellison syndrome). Unlike patients with duodenal ulcers, patients with gastric ulcers and functional dyspepsia have normal numbers of parietal cells and acid secretion, and the link with *H. pylori* is variable.

How gastric cancer develops

H. pylori also predisposes to gastric cancer, but patients have acid hyposecretion. This was once thought to be due to gastric body gastritis leading to atrophy and loss of acid-producing parietal cells. However, acid hyposecretion can in part be reversed by *H. pylori* eradication, suggesting that *H. pylori* causes gastric body gastritis/inflammation rather than permanent cell loss. Acid hyposecretion may be self-perpetuating because it supports the presence of *H. pylori* in the gastric body and so worsening gastric body gastritis, maintaining suppression of acid secretion. Acid hyposecretion predisposes to cancer by several mechanisms including impaired vitamin C absorption and overgrowth of bacteria in the stomach.

Is the location of *H. pylori* important in determining clinical outcome?

Given the above, the location of *H. pylori* (together with environmental, bacterial and host factors) thus determines whether a person with *H. pylori* infection tends towards a state of acid hypersecretion (predominantly antral gastritis) or acid hyposecretion (predominantly gastric body gastritis) and therefore the clinical outcome – asymptomatic infection, duodenal ulceration, gastric ulceration or gastric cancer.

Are there any implications from the presence of *H. pylori* for the use of PPIs?

Acid normally protects the gastric body from *H. pylori* colonisation. A PPI, by reducing acid production in the gastric body, can allow *H. pylori* to shift from the antrum to the gastric body and fundus causing a chronic active pangastritis that may progress to atrophic gastritis and, over time, gastric adenocarcinoma. PPIs thus have the potential to improve symptoms by reducing 'acid' symptoms but promote an increased risk of gastric cancer. Eradicating *H. pylori* should therefore be considered concurrently, although in practice this theoretical risk has not appeared to translate to substantial concern, and the widespread empiric use of PPIs appears to be relatively safe provided guidelines for when to test for *H. pylori* and when to contemplate endoscopy are followed.

What is Zollinger–Ellison syndrome?

This is peptic ulcer disease resulting from a gastrin-secreting adenoma, usually of pancreatic origin. It may be part of multiple endocrine neoplasia type 1 syndrome.

How is *H. pylori* infection diagnosed?

Invasive tests

Endoscopically, histology is very useful, culture unreliable and urease tests (CLO test) indicate only the presence or absence of infection.

Non-invasive tests

H. pylori elicits a local and systemic antibody response and circulating immunoglobulin (Ig) G antibodies can be detected, but individuals vary in antibody responses and titres fall slowly after eradication so serology cannot distinguish eradication from reinfection (there are no reliable IgM tests). Serology is thus not recommended in patients with uninvestigated dyspepsia. The ^{13}C-urea breath test is the most accurate non-invasive test with a sensitivity and specificity > 90% – urea is hydrolysed by *H. pylori* urease to carbon dioxide and ammonia and, following ingestion of carbon radio-labelled urea, radio-labelled carbon dioxide is detected in the breath of patients harbouring *H. pylori*. The faecal antigen test has a similar sensitivity and specificity to the urease breath test; however, PPIs should be stopped at least 2 weeks before and antibiotics at least 4 weeks before performing either of these tests because they can lead to false-negative results.

When is OGD indicated in patients with dyspepsia?

British Society of Gastroenterology guidelines suggest, for the first presentation of dyspepsia, the following.

People under 55 years

Those without alarm symptoms should have *H. pylori* serology checked (or urea breath testing). A positive *H. pylori* test is a good predictor of peptic ulcer and patients testing positive should receive *H. pylori* eradication therapy, and those with persisting symptoms after eradication therapy or patients testing negative whose symptoms persist after anti-secretory treatment should proceed to OGD. No action is required for patients rendered asymptomatic.

People 55 years or over or those with alarm symptoms

People 55 years or over with uncomplicated dyspepsia may receive empirical treatment first with OGD recommended if symptoms persist after 1–2 months, or they may proceed directly to OGD. People 55 years or over or patients with alarm symptoms should proceed to OGD. It is the 'gold standard' investigation of the upper gastrointestinal tract; its accuracy in detecting organic lesions is higher than 95%, and biopsies can be taken to diagnose *H. pylori* infection, precancerous conditions, and malignancy. Anti-secretory drugs should be stopped at least 2 weeks before OGD because treatment may heal early malignant ulcers and promote overgrowth of normal mucosa in sites of malignant tissue and mask early gastric cancer.

What empirical treatments are useful in dyspepsia?

Predominant epigastric pain or discomfort

Two strategies are available:

1. A non-invasive test for *H. pylori* and treatment of positive patients with eradication therapy (test and treat)
2. Empirical anti-secretory therapy (a Cochrane review showed that PPIs are the most effective anti-secretory drug).

The main benefit of test and treat over PPIs is that it cures most patients with underlying peptic ulcer and a small group of those with functional dyspepsia. However, the prevalence of *H. pylori* and peptic ulcer has decreased in the past decade, and it is not clear whether test and treat is still the best first-line strategy. PPIs are recommended as a second-line strategy in patients with persistent symptoms after *H. pylori* eradication and in those who are *H. pylori* negative.

Heartburn or regurgitation (GORD)

Test and treat is not recommended because these patients most likely have GORD, although evidence may be changing in favour of test and treat in reducing symptoms in patients with GORD. *H. pylori* eradication is not thought to heal oesophagitis, and in the presence of Barrett's oesophagus *H. pylori* might even, it has been suggested, protect against malignant transformation. However, guidelines suggest that eradication is sensible because of *H. pylori's* links with peptic ulceration and gastric cancer. The aim of GORD treatment is to control symptoms and prevent GORD-associated complications:

- Lifestyle changes include dietary changes (reducing fat, caffeine and alcohol), avoiding late meals and weight loss.
- Antacids/alginate combinations improve reflux symptoms but do not heal oesophagitis and are indicated for very mild symptoms where step-up treatment is not necessary.
- PPIs are pro-drugs activated in the parietal cell, inhibiting the final pathway of acid secretion and suppressing acid production for several days. Histamine-2-receptor antagonists (H2A) reversibly bind H2 gastric parietal cell receptors. Both H2As and PPIs heal and prevent relapse of oesophagitis, although PPIs are superior to H2As and prokinetic agents. Patients with typical reflux symptoms who do not respond to initial courses of PPIs may have an alternative diagnosis, inadequate acid suppression or functional heartburn. If symptom control is not

achieved after 4 weeks it may be worth extending PPI therapy to 2 months.

- Prokinetic agents with correction of the anti-reflux barrier is the most obvious target for the treatment of GORD, but existing drugs such as domperidone have not shown promise. GABA-B agonists may have future potential.

How are patients managed following OGD investigation?

Biopsy specimens should be taken from the antrum and the body of the stomach for diagnosing *H. pylori* infection.

Oesophagitis or peptic ulceration

OGD may show oesophagitis or peptic ulceration, which should be treated with PPIs, together with *H. pylori* eradication for duodenal ulcers, gastric ulcers not due to NSAIDs, and mucosa-associated lymphoid tissue lymphoma; eradication is not indicated in peptic ulcers due to NSAIDs. However, most patients have no structural lesion.

No structural lesion and GORD symptoms

Patients should be treated with PPIs. Eradicating *H. pylori* does not usually provide symptom relief in these patients, but may be considered because it does not worsen symptoms and may have other long-term benefits. The rationale for surgery in GORD is to reverse the physiological LOS abnormalities associated with GORD, achieved by lengthening and increasing the proportion of intra-abdominal LOS. The most common technique is the Nissen fundoplication, where the gastric fundus is wrapped around the distal oesophagus. There is no statistical difference between outcomes of medical therapy (PPI or H2A) and surgery for GORD, but, since there is operative risk, surgery is considered second to medical therapy.

No structural lesion and functional dyspepsia

Eradication of *H. pylori* should be the first-line treatment; 10% of patients with functional dyspepsia benefit from *H. pylori* eradication. PPIs should be given to *H. pylori*-negative patients and those who fail to respond to eradication therapy, although reassurance of the benign nature of symptoms may be the best treatment overall.

For which conditions should *H. pylori* infection definitely be treated?

Several conditions have been linked to *H. pylori* infection, for which eradication is beneficial (Table 2.6).

Table 2.6 Conditions linked to *Helicobacter pylori* infection for which eradication is beneficial

Condition linked to *H. pylori* infection	Benefits of *H. pylori* eradication
Peptic ulcer (active or confirmed history)	Healing; prevention of recurrence; prevention of recurrent bleeding
Gastric mucosa-associated lymphoid tissue lymphoma (low grade)	Durable remission
Uninvestigated dyspepsia without alarm symptoms	Management of symptoms
Patient at increased risk of gastric cancer (first-degree relative of patient with gastric cancer; after gastric cancer resection)	Prevention of development or recurrence of gastric cancer

The association between gastric cancer and *H. pylori* infection is strong but it is not known whether eradicating *H. pylori* infection reduces the risk of developing gastric cancer.

How can *H. pylori* eradication be confirmed?

The urea breath test is the optimum test to confirm eradication. Eradication should be confirmed at least 4 weeks after treatment ends. If positive, an alternative eradication regimen could be used. Eradication of *H. pylori* should always be confirmed in cases where a duodenal ulcer has bled, to ensure complete epithelialisation of the crater. Invasive methods to confirm *H. pylori* eradication should be limited to cases where repeat OGD is indicated (such as gastric ulcer, where OGD is mandatory, with initial targeted biopsies of the rim and base, and repeat endoscopy performed 8 weeks later to confirm healing and to obtain biopsies from the original ulcer site).

List some causes of upper gastrointestinal bleeding

Causes and frequencies are shown in Table 2.7. Small bowel (e.g. angiodysplasia, investigated by wireless capsule endoscopy or computed tomographic angiography) and right-sided colonic disease may present with melaena.

Table 2.7 Causes of upper gastrointestinal bleeding

Cause	Frequency (%)
Peptic ulceration	35–50
Oesophagitis	20–30
Erosive disease (duodenitis, gastritis, erosions)	10–20
Varices	5–10
Mallory–Weiss tear	2–5
Neoplasm	2–5
Vascular malformations	2–3
Aorto-gastrointestinal fistula	< 1

Table 2.8 The Rockall score

	0	1	2	3	Score
Age	< 60	61–79	≥ 80	–	Pre-endoscopy score (maximum 7): 0–2 low risk (endoscopy routine), 3–5 moderate risk (endoscopy within 24 hours), 6–7 high risk (endoscopy with 8 hours)
Shock	SBP ≥ 100 HR ≤ 100	SBP ≥ 100 HR ≥ 100	SBP ≤ 100 HR ≥ 100	–	
Comorbidity	Nil	Nil	e.g. ischaemic heart disease	e.g. liver or renal disease, malignancy	
Diagnosis	Nil or Mallory–Weiss tear	All other diagnoses	Malignancy	–	A post-endoscopy score can now be derived (maximum 11, 2 predicting 0.1% mortality and 8 predicting 41% mortality)
Major endoscopic stigmata of recent haemorrhage	Clean base or dark spots	–	Ooze, adherent clot, non-visible bleeding vessels, active spurting	–	

HR, heart rate; SBP, systolic blood pressure.

How should peptic ulcer bleeding be managed?

PPIs appear not to significantly reduce re-bleeding or need for surgery. Several endoscopic modalities are available to achieve haemostasis for bleeding ulcers. Combination therapy of epinephrine (adrenaline) injection with mechanical methods of haemostasis reduce re-bleeding compared with a single treatment. A minority of patients with refractory bleeding need surgical oversewing of an artery or partial gastrectomy.

How might you assess risk in a patient who presents with upper gastrointestinal bleeding?

Haematemesis (bright red, dark clots or coffee-ground) or melaena indicate an upper gastrointestinal bleed. The Rockall score is a clinical and endoscopic predictor of risk of re-bleeding and death (Table 2.8). The Glasgow–Blatchford score (Table 2.9) does not rely on endoscopy; its place is more to predict the need for intervention than to predict mortality, and so has greater emphasis in less severe bleeding.

Can bradycardia be a sign of acute haemorrhage?

A normal or low heart rate and hypotension may occur in acute haemorrhage, often after gastrointestinal surgery. The first response to maintain arterial pressure despite a falling cardiac output involves tachycardia and baroreceptor reflex vasoconstriction. A second phase, however, occurs when about a third of the circulating volume has been lost, in which sympathetically mediated vasoconstriction and cardiac drive fall abruptly and cardiac vagal drive increases.

Table 2.9 The Glasgow–Blatchford score

Variable		Score (≥ 5 predicts need for intervention)
Urea (mmol / l)		
> 6.5, < 8		2
≥ 8, < 10		3
≥ 10, < 25		4
≥ 25		6
Haemoglobin (g / dl)		
Men	Women	
≥ 12, < 13	≥ 10, < 12	1
≥ 10, < 12		3
< 10	< 10	6
SBP		
100–109		1
90–99		2
< 90		3
HR > 100		1
Melaena		1
Syncope		2
Liver disease		2
Cardiac failure		2

HR, heart rate; SBP, systolic blood pressure.

CASE 2.4 DYSPHAGIA

Candidate information

Role

You are a doctor in the gastroenterology clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr James Morton, aged 62 years

Thank you for seeing this gentleman who reports difficult swallowing over the last 3 months. He is now frequently vomiting and his routine blood tests show he has a sodium of 130 mmol/l and potassium of 2.9 mmol/l. His renal and liver functions are normal and he is not anaemic. A routine chest X-ray is reported as showing a hugely dilated oesophagus. Please see and advise on urgent endoscopy.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr James Morton is a 62-year-old retired, rather stoical, farmer with a history of reflux symptoms treated by his GP with omeprazole for the last 12 months (although he has taken it sparingly). He takes no other medications. For the last 3 months he has had difficulty swallowing and some vomiting to the extent that he can become dehydrated. He has lost around 10 kg in weight, but attributes this to not being able to eat. He is otherwise previously well. He wishes to avoid further investigation or treatment if possible because he believes 'treatment does more harm than good and these things are best left to nature to heal'.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

Dysphagia refers to delay in the passage of solids or liquids from mouth to stomach. It should be distinguished from odonyphagia, which is discomfort or pain on swallowing hot or cold liquids. The history should take a similar approach to that of dyspepsia, in particular asking about alarm features:

- **A** anaemia
- **L** loss of weight (a worry, prompting check of inflammatory markers) or anorexia
- **A** abdominal mass
- **R** recent onset of progressive symptoms
- **M** melaena or haematemesis
- **D** dysphagia.

Although attempted localisation can be misleading clinically, it is useful to separate those causes that predominantly affect the pharynx and proximal oesophagus (high dysphagia) from those that affect the oesophageal body and oesophago-gastric junction (Table 2.10).

Swallowing assessment

Ask about the following factors that can influence swallowing:

- Medications
- Nutritional intake
- Teeth
- Posture
- Neck problems, e.g. cervical spondylosis
- Neck or limb weakness
- Respiratory problems.

Patient perspective

Explore his reasons for preferring to avoid treatment and explain the possible causes, and risks if left untreated.

Past medical history

The history of oesophagitis is important, even though he has taken a proton pump inhibitor, as it can transform to oesophageal malignancy.

Drug and allergy history

Ask specifically about non-steroidal anti-inflammatory drugs or corticosteroids.

Family history

Relevance here is unlikely.

Social history

Ask about alcohol and smoking – both risk factors for peptic ulceration.

Discussion

What are the phases of swallowing?

Swallowing has cortical input and is mediated in the brainstem, which receives sensory information from the tongue, pillars of fauces and pharynx. Following pre-oral anticipation of food there are three phases of swallowing: oral, pharyngeal and oesophageal.

Table 2.10 Causes of dysphagia

Type of dysphagia	Causes	Pointers in history to possible causes
Low (oesophageal)	Oesophageal or oesophago-gastric junction malignancy GORD with or without stricture Oesophagitis secondary to candida, cytomegalovirius or herpes simplex virus (consider AIDS) Oesophageal motility disorders, e.g. achalasia, diffuse oesophageal spasm	Malignancy suggested by alarm symptoms and short history with dysphagia for solids more than liquids Otherwise, achalasia more likely, patients often describing chest pain and minor dysphagia Reflux-induced strictures common, often without a history of GORD Barrett's oesophagus often characterised by diminished oesophageal sensitivity and lack of pain
High (pharyngeal)	Stroke Parkinson's disease Dementia Bulbar palsy, e.g. motor neurone disease, myasthenia gravis Oropharyngeal malignancy Crico-oesophageal spasm Pharyngeal pouch	Known neurological disease, e.g. multiple sclerosis, motor neurone disease Tendency for spillage into trachea on eating, causing coughing or choking

AIDS, acquired immunodeficiency syndrome; GORD, gastro-oesophageal reflux disease.

SUMMARY BOX – ASSESSMENT AND PLAN

- Malignancy must be excluded. Achalasia, however, is very likely given the distended oesophagus on chest X-ray.
- A full examination is important; ear, nose and throat examination is often indicated.
- Initial tests for dysphagia should always include a full blood count, haematinics, inflammatory markers, renal and liver function, calcium and thyroid function and a chest X-ray.
- Assessment by a speech and language therapist should be requested.
- An oesophagogastroduodenoscopy should be arranged urgently.

Oral phase

This involves propulsion of the bolus backwards along the tongue past the fauces and into the pharynx, triggering the swallow reflex and initiation of the pharyngeal phase. The tongue tip and blade press the bolus against the hard palate, the sides of the tongue rising in smooth progression from front to back to force the bolus along a central groove, and swallowing is triggered when the bolus reaches the tongue base, the soft palate rising to occlude the nasopharynx and avoid nasal regurgitation. In the oral phase the airway is open and the cricopharyngeal sphincter closed. The timing from the start of lingual peristalsis to trigger of swallow is normally < 1 second. Once swallow is triggered, voluntary control is surpassed.

Pharyngeal phase

This is rapid, also < 1 second. It involves movement of the bolus through the pharynx by pharyngeal muscle contraction, with elevation of the larynx to fit under the tongue base, the vocal cords coming together and the epiglottis covering the laryngeal opening. All of this is seen externally as the Adam's apple rising to protect the airway. The bolus may sit transiently in the valleculae then pharyngeal peristalsis squeezes it downwards as the cricopharyngeal sphincter relaxes to admit the bolus into the oesophagus. The soft palate and larynx are then lowered and breathing recommences.

Oesophageal phase

This is reflexic, not under voluntary control, and no longer speech and language therapy territory!

Outline your approach to managing dysphagia

This is outlined in Box 2.9.

What is the role of speech and language therapists in a swallow assessment?

Bedside screening (e.g. water swallow test) to identify patients at risk of aspiration can be carried out by any doctor. It can miss silent aspiration and pharyngeal function can only be inferred.

Referral to a speech and language therapist is appropriate in patients who are alert, able to sit upright for at least 15 minutes, have a stable chest status and in whom there is evidence of oral or facial weakness or sensory disturbance, a wet/gurgly voice or drooling.

Speech and language therapists more fully assess swallow stages and safety and may recommend videofluoroscopy (the gold standard for identifying aspiration and features of dysphagia).

A full history takes account of the normal level of independence with feeding to avoid overly optimistic expectations. Problems with co-operation and cognition (e.g. awareness of spoons, cups and straws in patients with dyspraxia or dementia or volition to eat or swallow in dementia), communication (dysphasia, dysarthria, Box 2.9 **Management of dysphagia**

Low (oesophageal) dysphagia

- Endoscopy is the investigation of choice. Where endoscopy is normal, ambulatory pH studies and oesophageal manometry and occasionally oesophageal provocation tests are indicated.
- A benign stricture is confirmed histologically and managed by dilation if possible and maintenance treatment with a proton pump inhibitor. Oesophagitis due to infection warrants specific treatment.
- An oesophageal or gastric tumour is managed operatively by resection in fit patients where there is no evidence of metastases, stenting or laser treatment, or pure palliation.
- Achalasia may be detected as a widened oesophagus on chest X-ray and is characterised by absent distal oesophageal peristalsis and abnormal relaxation of the lower oesophageal sphincter; it may be managed by pneumatic balloon dilatation, often repeatedly, or, failing this, Heller's myotomy of the lower oesophageal sphincter.
- Diffuse oesophageal spasm is rare and characterised by simultaneous contractions seen on barium swallow as a 'corkscrew' oesophagus.

High (pharyngeal) dysphagia

- Radiology is generally more rewarding than endoscopy. Most problems are due to failure of pharyngeal contraction or cricopharyngeal relaxation or both and cineradiography with barium (liquid or bread soaked in) can give functional as well as anatomical information.
- A pouch or pharyngeal bar can be managed by surgical myotomy of the overactive cricopharyngeus, sometimes with pouch excision.
- Neuromuscular problems (e.g. post-stroke) may require consideration of percutaneous endoscopic gastrostomy feeding.

dysphonia), vision, hearing, dentition and gross motor function of head and neck and upper limbs are all relevant. Fatiguability is important to elicit. Respiratory function and clearance of secretions are important in assessing risk of aspiration (e.g. immediate or delayed reflexive cough, audible pharyngeal crackles, wet/gurgly vocal quality, respiratory difficulty), as is oral hygiene.

Manual assessment of the pharyngeal phase can be performed by observing initiation of tongue movement and feeling the rise, forward motion and fall of the larynx.

If considered safe to proceed, oral handling of fluid and diet is assessed. Some patients who aspirate thin fluids may not with thickened fluids.

In Parkinson's disease, for example, there is a prolonged oral phase with considerable rocking and rolling of the bolus in the mouth. Multiple swallows may be needed to clear each mouthful with retention of bolus in the mouth. Pharyngeal motility, criopharyngeal opening and oesophageal motility may all be reduced.

Overall, a decision is made as to whether swallow is safe or poses a risk of aspiration.

Therapeutic measures include advice on food type, texture, consistency, size and preferences and positions for feeding. Nasogastric or gastrostomy feeding may be necessary.

CASE 2.5 ABDOMINAL PAIN

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Edward Bertram, aged 80 years
> Mr Bertram has developed subacute abdominal pain over the past few days. I phoned the surgical team, but because he has a complex history, they would prefer you to take the patient and advise on his medical management. They are happy to be consulted about his pain if you suspect a surgical cause.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Edward Bertram is an 80-year-old man who has just been admitted to hospital because of worsening episodes of abdominal pain over the past few days. Over the past few months he has noticed dull pain after meals centred on the umbilicus. Sometimes this is associated with blood-tinged diarrhoea. The pain tends to occur mostly with bigger meals, and not with snacks, although he has not noticed any association with particular types of food. He has a past medical history of ischaemic heart disease, atrial fibrillation and type 2 diabetes. He gets angina about twice weekly. He also has Crohn's disease, having had a terminal ileal resection 8 years ago, but the disease has not been symptomatically active for 2 years. He takes aspirin 75 mg daily, bisoprolol 5 mg daily, simvastatin 40 mg daily, perindopril 4 mg daily and mesalazine. He is an ex-heavy smoker. He lives with his wife, who has advanced dementia, and he is her only carer. He is very worried about who will look after her because no other family members are nearby and he was rushed into hospital by ambulance before care could be arranged. He has good neighbours, and needs to contact them.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Determine the type of abdominal pain.** There are two types of acute abdominal pain (Table 2.11).

■ **Determine the site of abdominal pain.** These two types of pain may occur at one of three main sites in the abdomen because the brain receives visceral pain impulses from each of the three embryological components of the gut (Table 2.12).

■ **Integrate the above two pieces of information to form likely diagnoses.** This knowledge of types and sites of pain can direct you towards common causes:

- *Colicky epigastric pain* is frequently the result of biliary colic.
- *Continuous epigastric pain* is more likely to be the result of peptic ulcer disease or pancreatitis.
- *Colicky periumbilical pain* in an elderly patient with weight loss and anaemia is right-sided colonic cancer unless proven otherwise. In a young patient with episodic diarrhoea, constipation and bloating, without alarm symptoms, it may well be irritable bowel syndrome.
- *Continuous periumbilical* pain may be caused by peritonitis resulting from a perforated viscus, mesenteric ischaemia or visceral peritoneal irritation in appendicitis.
- *Colicky suprapubic pain* with alteration in bowel habit may be the result of colorectal cancer, inflammatory bowel disease or irritable bowel syndrome.
- *Continuous pelvic pain* in a young woman may be caused by pelvic inflammatory disease, an ovarian cyst or ovarian torsion.
- *Visceral pain* is often a vague, colicky midline pain, because it arises from visceral peritoneum in communication with a viscus. Continuous pain may be of visceral or parietal origin or both.
- *Parietal pain* tends to be more localised because the parietal peritoneum is innervated by spinal nerve roots that have specific sensory cortical representation. Hence, appendicitis, biliary colic and diverticulitis may all start as midline visceral pain but further localise to the right iliac fossa, right hypochondrium and left iliac fossa, respectively, if the parietal peritoneum becomes inflamed. The kidneys and ureters (retroperitoneal structures) have parietal or spinal innervation from T8 to L1; hence ureteric colic may be perceived as progressing from the loin (T8 dermatome) to the groin (L1 dermatome).

  Pain may also arise from structures outside the abdominal cavity such as the abdominal wall or in a nerve root as in shingles.

■ **Be alert to typical patterns of common conditions.** These are outlined in Table 2.13.

Table 2.11 Two types of acute abdominal pain

Type of pain	Cause
Colicky (gripping, often severe and comes in waves)	Abnormally strong peristalsis of a hollow viscus triggered by either obstruction (e.g. stone, tumour, hernia) or irritation (e.g. gastroenteritis)
Continuous (present lying still and exacerbated by movement)	Inflammation, triggered by infection, ulceration, peritonitis or ischaemia

Table 2.12 Sites of abdominal pain

Derivation	Site of pain
Foregut (stomach, proximal duodenum, gall bladder, biliary tree and pancreas)	Epigastric
Midgut (distal duodenum to two-thirds across the transverse colon)	Periumbilical
Hindgut (last third of transverse colon to rectum, and gynaecological areas of the pelvis, derived from the cloacal sac)	Suprapubic / pelvic

Table 2.13 Common causes of abdominal pain and their symptoms

Cause	Symptoms
Biliary colic	Intense, right upper quadrant pain With fever and tenderness indicates acute cholecystitis
Pancreatitis	Epigastric / central abdominal pain radiating to the back Pain could also be ruptured abdominal aortic aneurysm!
Bowel obstruction	Constipation Colicky abdominal pain Distension Vomiting
Perforated viscus	Progressive pain exacerbated by minimal movement Rebound tenderness
Mesenteric ischaemia / infarction	Pain with or without rectal bleeding Usually vascular risk factors
Diverticulitis	Left iliac fossa discomfort ± fever History of constipation
Ureteric colic	Intense, intermittent pain from loin to groin Often haematuria
Abdominal aortic aneurysm rupture	Leaks may be either acute, with an expansile pulsatile mass, or slow

Patient perspective

Explore any ideas, concerns and expectations.

Past medical history

Take a full history about the Crohn's disease and its treatments.

Drug and allergy history

He is taking aspirin rather than warfarin for atrial fibrillation. Determine whether there are reasons for this.

Family history

The family history is probably irrelevant.

Social history

The level of care required by his wife should be explored, and, crucially, whether care needs to be put in place immediately for her own safety.

SUMMARY BOX – ASSESSMENT AND PLAN

- The symptoms and risk factors are in keeping with mesenteric ischaemia. A flare-up of Crohn's disease is possible.
- He should have a full examination and a full set of haematobiochemistry tests, including glucose and inflammatory markers. A raised serum lactate may suggest infarcted tissue, but may be normal in ischaemia. Chest and abdominal radiographs are important, as is an electrocardiogram to determine the rhythm.
- A surgical opinion should be sought unless it is very clear that he has a flare-up of Crohn's disease.

Discussion

What are the major arteries supplying the small intestine and colon?

The superior mesenteric artery (SMA) supplies the small intestine and ascending and transverse colon via the ileocolic, jejunal, ileal, right colic and middle colic arteries. The inferior mesenteric artery (IMA) supplies the left colic artery, marginal artery and sigmoid arteries.

What is meant by the term acute mesenteric ischaemia?

Acute mesenteric ischaemia or infarction implies impaired blood flow in the mesenteric arterial or venous systems and is most often caused by thrombotic or embolic disease (Table 2.14).

Table 2.14 Causes of acute mesenteric ischaemia

Arterial occlusion (50%)	Superior mesenteric artery embolus (mural thrombus, atrial fibrillation, valve lesion, cholesterol embolus) Thrombotic (atherosclerosis, acute obstruction on background of chronic mesenteric ischaemia) Dissecting aortic aneurysm Vasculitis Fibromuscular dysplasia Trauma Endotoxic shock
Non-occlusive (20–30%)	Cardiac failure Septic shock
Venous occlusion (5–15%) (usually small intestine)	Prothrombotic disorder Inflammation Neoplasm Drugs
Extravascular causes	Incarcerated hernia Volvulus Adhesions

How does acute mesenteric ischaemia present?

It often presents non-specifically, with abdominal pain. Classically, the abdominal pain is disproportionately exaggerated relative to signs and persists and may evolve into an acute abdomen with distension, guarding (rigidity), tenderness, fever and signs of circulatory compromise. Blood loss per rectum occurs in a minority of patients.

How does chronic mesenteric ischaemia present?

Chronic mesenteric ischaemia ('intestinal angina') is often characterised by post-prandial pain, sitophobia (fear of eating) and weight loss. Pain may be minimal at the outset but progress over weeks. Obstruction of at least two or three major splanchnic arteries usually occurs before symptoms are evident. When thrombosis affects the portal or splenic veins, the initial presentation may be variceal bleeding, ascites or splenomegaly.

What do you know about ischaemic colitis?

Blood supply to the colon arises from branches of the SMA and IMA, and the rectum also receives a supply from the haemorrhoidal arteries, branches of the internal iliac. Ischaemic colitis results from hypoperfusion or thrombotic or embolic occlusion (although the cause is often not identified) and is the most common ischaemic injury to the gastrointestinal tract. It occurs mostly in older people and typically affects watershed areas (splenic flexure, rectosigmoid junction), and a specific event or vascular lesion is often not identified. It typically presents with mild abdominal pain of sudden onset, usually accompanied within 24 hours by haematochezia/bloody diarrhoea. Investigation is with abdominal radiology, computed tomographic (CT) angiography or colonoscopy. It usually settles with supportive treatment. In younger patients, vasculitis, sickle cell disease, prothrombotic disorders and drugs including cocaine may all be causes.

Which investigations may aid diagnosis of intestinal ischaemic disorders?

Metabolic (lactic) acidosis may be a clue to severe ischaemia. Plain X-rays are usually non-specific but can help exclude perforation or obstruction; the classic thumbprinting of submucosal haemorrhage or oedema resulting in focal mural thickening is a late sign. Intramural pneumatosis may be seen in advanced infarction. Ultrasound may detect mesenteric stenosis. CT and magnetic resonance angiography are non-invasive investigations.

What treatments are available?

Surgical revascularisation remains the treatment of choice for mesenteric ischaemia, but thrombolytic therapy and vascular interventional radiography have a growing role. Indications for surgical management of ischaemic colitis include peritoneal signs, massive haemorrhage, sepsis, stricture formation and persistent symptoms.

How should biliary sepsis be managed?

It should be suspected with pain in the right upper quadrant, fever and deranged liver enzymes, but may be covert. Antibiotics should be administered. An ultrasound scan is important, and magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography may be considered if gallstones or any other underlying obstructive lesion is suspected, to further diagnosis or provide endoscopic treatment.

CASE 2.6 ALTERED BOWEL HABIT AND LOWER GASTROINTESTINAL BLEEDING

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Ms Louise Musgrove, aged 30 years

This lady has a 4-month history of watery diarrhoea. There is associated mucus. She was previously well. I would be grateful for your further assessment and append her laboratory results.

Yours sincerely

Full blood count normal except for mild hypochromic microcytic anaemia, liver function tests including albumin normal, erythrocyte sedimentation rate 45, stool microscopy and culture negative for bacteria, ova, cysts and parasites.

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Ms Louise Musgrove is a 30-year-old woman who has had watery diarrhoea, passing at least six stools per day, sometimes with mucus, for 4 months. She is usually well. Ten months ago she travelled through Australia and the Far East with friends, but her trip was punctuated by a 3-week episode of gastroenteritis for which she took a self-administered course of doxycyline. Symptoms seemed to settle, recurring transiently a month or two later, but then she was well for a few months before symptoms recurred with more severity than previously. Her GP has checked stool cultures (negative) and tried a further course of doxycycline but this time without effect. She has lost around 8 kg in weight since before travelling. Before travelling she was very well. She works as a solicitor. She does not smoke. Her sister has type 1 diabetes, an aunt has coeliac disease and a cousin undergoes regular surveillance after treatment for colon cancer diagnosed at an early age.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Determine the type of diarrhoea.** Diarrhoea is difficult to define. Definitions sometimes refer to > 200 ml of stool per day or to increased stool frequency and decreased consistency. It may be acute (less than 2 weeks in duration), subacute (2–4 weeks) or chronic (> 4 weeks), and is predominantly a result of small bowel disease (often larger volume, pale, with steatorrhoea) or large bowel disease (often smaller volume with blood or mucus). Small bowel causes of diarrhoea may be classified as secretory (e.g. infectious, malabsorptive), osmotic (e.g. osmotic laxatives) or the result of altered motility (e.g. hyperthyroidism, autonomic neuropathy). Secretory symptoms tend to persist with fasting.

■ **If symptoms suggest a small bowel cause.** Consider the common causes of malabsorption in the UK (Box 2.10).

Box 2.10 **Malabsorption**

Symptoms

Malabsorption typically causes steatorrhoea, weight loss and fatigue, together with symptoms resulting from deficiency of essential nutrients and vitamins such as iron, folate and calcium.

Causes

Common causes in the UK include:

- Coeliac disease (a range of other presentations are common)
- Cystic fibrosis (diagnosed in childhood)
- Post-enteritis enteropathy
- Giardiasis
- Chronic pancreatitis, e.g. alcohol; autoimmune form increasingly recognised.

Broadly, malabsorption may be the result of a lack of pancreatic enzymes (cystic fibrosis, chronic pancreatitis), lack of solubilising bile salts causing failure of micelle formation (obstructive liver disease, small bowel bacterial overgrowth), decreased transit time (post-gastrectomy, 'short-gut syndrome', thyrotoxicosis), small bowel mucosal pathology impeding absorption (coeliac disease, post-infectious enteropathy, Whipple's disease, Crohn's disease, intestinal lymphangiectasia, lymphoma) or intestinal infestation (giardiasis). Small bowel bacterial overgrowth may be secondary to diverticulae, blind loops, obstruction (Crohn's disease), infiltration (systemic sclerosis), poor motility (pseudo-obstruction, diabetes) or immunodeficiency (immunoglobulin A deficiency).

■ **If symptoms suggest a large bowel cause.** Consider inflammatory bowel disease (ask about blood, mucus, pus, slime) and colorectal cancer (CRC), and ask about alarm symptoms. Remember that irritable bowel syndrome is characterised by episodes of constipation and diarrhoea with abdominal bloating in a younger adult without alarm symptoms. In older patients, diverticular disease and mesenteric ischaemia are common. *Candida* can cause diarrhoea on a prolonged antibiotic course in hospital.

Patient perspective

Ascertain her ideas, concerns and expectations.

Past medical history

Ask about thyroid disease, coeliac disease, diabetes and previous surgery.

Drug and allergy history

Ask about recent antibiotics.

Family history

Note the family history of CRC at an early age.

Social history

Ask about alcohol intake (chronic pancreatitis, often presenting as relapsing steatorrhoea and back pain). Ask about foreign travel or unwell contacts (infectious causes).

Box 2.11 **Investigations for diarrhoea with a suspected small bowel cause**

- Full blood count for anaemia, with iron, folate and vitamin B12 levels
- Inflammatory markers, e.g. erythrocyte sedimentation rate, C-reactive protein
- Urea, electrolytes, liver function tests (especially albumin) and calcium (hypocalcaemia and concurrent hypomagnesaemia is a very important cause–effect vicious cycle of diarrhoea)
- Stool microscopy and culture for bacteria, ova, cysts and parasites
- Tests for bacterial overgrowth (sometimes jejunal aspirates for bacterial quantification)
- Endoscopy and jejunal biopsy; wireless capsule endoscopy is now possible for small bowel visualisation

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ Post-enteritis enteropathy is a leading contender given that she was previously well and that her symptoms started with gastroenteritis overseas; persistent infection due to, for example, *Giardia*, should be excluded with multiple stool cultures.
- ◆ Coeliac disease should be considered given the strong family history of autoimmune disease.
- ◆ Haematobiochemistry should include thyroid function and markers of malabsorption.
- ◆ Colonoscopy should be considered relatively urgently to exclude inflammatory bowel disease and, given the family history, colorectal cancer.

Discussion

List some investigations for diarrhoea with a suspected small bowel cause

These are listed in Box 2.11.

Where are the major nutrients absorbed, including iron, vitamin B12 and folate?

The small bowel is the main site of absorption of nutrients, notably carbohydrates, fats (triglycerides split into fatty acids and glycerol by pancreatic lipase and fatty acids are solubilised by bile salts from the liver to form water-soluble micelles) and proteins, which enter the circulation via the portal vein. Iron is absorbed in the upper small bowel, folate in the duodenum and jejunum and vitamin B12, bound to intrinsic factor, mainly in the terminal ileum.

What do you know about coeliac disease?

Coeliac disease is discussed in Box 2.12.

Box 2.12 **Coeliac disease**

Cause

Coeliac disease is the result of sensitivity to the gliadin component of gluten causing villous atrophy in genetically susceptible individuals. Tissue transglutaminase (TTG) may modify gliadin and act as an autoantigen. Coeliac disease has a wide range of presentations, is more common than previously recognised and confers an increased risk of malignancy, especially small bowel lymphoma; colorectal cancer is increased and anaemia in coeliac disease warrants colonoscopy.

Symptoms

Coeliac disease may cause diarrhoea, malabsorption with steatorrhoea, weight loss and growth retardation. A wide spectrum of disease activity has been recognised. Covert symptoms include malaise and recurrent aphthous ulceration. It may cause hyposplenism. It may also present as unexplained folate or iron deficiency anaemia (now the commonest presentation). It is important to ask about itchy rashes (dermatitis herpetiformis is rare, however) and bone pain (osteomalacia). Ataxia is not uncommon. Autoimmune associations other than dermatitis herpetiformis include Addison's disease, thyroid disease, autoimmune hepatitis, primary biliary cirrhosis and type 1 diabetes.

Diagnosis

The gold standard test is jejunal biopsy for villous atrophy. Patients should undergo re-endoscopy after a period of gluten exclusion to confirm villous regeneration. Other causes of villous atrophy include Whipple's disease and small bowel lymphoma. Antiendomysial and anti-TTG antibodies are highly specific and nearly always positive. Antigliadin and antireticulin antibodies may be positive.

Treatment

A strict diet with complete exclusion of gluten-containing flour from wheat, rye, oats and barley is essential. Folate, iron and calcium supplements may be needed. Lifelong annual review should include assessment of symptoms, body mass index, haemoglobin, ferritin, folate, albumin, autoantibodies and osteoporosis risk (with bone densitometry for post-menopausal females and males aged over 55 years).

What are the infectious causes of acute watery diarrhoea?

This is usually the result of small bowel disease, often viral, such as norovirus with an incubation period of 24–48 hours, or the result of *Escherichia coli*. Enterotoxigenic *E. coli* is a common cause of 'traveller's diarrhoea'. Cholera is a very important cause worldwide. Preformed toxins in food also cause acute watery diarrhoea, such as toxins from *Staphylococcus aureus* or *Bacillus cereus* provoking symptoms within 6 hours (tending to provoke vomiting more than diarrhoea) or toxins from *Clostridium perfringens* within 8–12 hours.

What are the infectious causes of chronic watery diarrhoea?

This is most commonly caused by *Giardia lamblia* (giardiasis). Cryptosporidiosis, microsporidiosis and isosporiasis should be considered in immunosuppressed patients. Non-infectious causes, especially coeliac disease, must be considered.

What are the infectious causes of acute bloody diarrhoea?

This implies invasive disease, usually colitis. The broad term for this presentation is 'dysentery'. The most common causes in the UK are non-typhoidal *Salmonella* spp., *Campylobacter jejuni* and *Shigella*, with incubation periods of 1–5 days. The enteric fevers *Salmonella typhi* and *S. paratyphi* should be considered following travel to an area of risk. *Vibrio parahaemolyticus* should be considered with a history of shellfish ingestion.

What are the infectious causes of chronic bloody diarrhoea?

This may be caused by amoebic dysentery. The commonest non-infectious cause is inflammatory bowel disease.

Are there any advances in antimicrobial treatment of diarrhoea?

Diagnosis still falls heavily on stool microscopy and culture, but faecal antigen- and DNA-based tests are advancing. Whilst rehydration remains the most important treatment step, quinolones may be used in traveller's diarrhoea, the non-absorbable antibiotic rifaximin is very effective in traveller's diarrhoea and the broad-spectrum antimicrobial nitazoxanide is useful in cryptosporidiosis, and sometimes in giardiasis, amoebiasis and *Clostridium difficile* infection. There is increasing evidence for probiotics and prebiotics in treating and preventing a range of intestinal infections.

Why is norovirus important?

Norovirus is the most common cause of institutional, particularly health-care-associated, outbreaks of gastroenteritis and is difficult to contain. It is now also a common cause of 'food poisoning'.

Why is Shiga-toxin-producing *E. coli* (STEC) important?

Although infrequent, STEC carries the potentially serious complication of haemolytic uraemic syndrome.

What is *C. difficile*?

C. difficile is a Gram-positive, spore-bearing anaerobe that is widely distributed in the environment. It dies rapidly in the air, but its spores can survive indefinitely (for a thousand years or more). It has two exotoxins: toxin A an enterotoxin, and toxin B a cytotoxin, the latter causing inflammation in the colon.

Why is *C. difficile* important?

C. difficile is increasing in incidence, with increasingly virulent strains. It is carried asymptomatically by 2% of healthy adults and up to 10–20% of older hospitalised patients. The clinical spectrum is diverse. It is frequently ingested from soil, beaches or rivers, dies rapidly in gastric acid, but may asymptomatically colonise the gut or cause diarrhoea, colitis, pseudomembranous colitis, megacolon and death. Protective factors include carriage on admission to hospital, high serum antibody titres to toxin A, and good health. In recent years a hypervirulent strain with increased resistance, NAP1/027, has emerged, producing higher levels of toxins A and B and an extra toxin (binary toxin).

When is *C. difficile* likely to become more pathogenic?

It is more likely to become pathogenic with mucosal damage and alteration in gut flora, states often induced by antibiotics (may be many months antecedent) or foods containing antibiotics. Risk factors for *C. difficile*-associated diarrhoea (CDAD) include age, comorbidity, prolonged hospital stay, multiple antibiotics and length of courses, nasogastric tubes, endoscopy and proton pump inhibitors (these drugs may double the risk of CDAD).

What are the symptoms of CDAD?

C. difficile causes a spectrum of disease from asymptomatic gut colonisation through to fulminant colitis. Secretory diarrhoea and acute inflammation lead to ulcers on the mucosal surface, and proteins, mucous and inflammatory cells leak out forming the characteristic 'pseudomembrane' appearance in severe disease.

How is CDAD diagnosed?

Diagnosis is by detection of toxin, most commonly by immunoassay, which has 85–95% sensitivity for toxins A or B. Two negative results traditionally cast doubt on the diagnosis, but more samples might need to be analysed before excluding, with CDAD specifically stated as a possibility; this is because CDAD is now the commonest cause of diarrhoea in hospital. Culture of *C. difficile* is not specific for disease because of asymptomatic carriage and non-toxicogenic strains. Typing, if needed, may be confirmed by polymerase chain reaction, 001 being the most common.

Which haematobiochemical disturbances are common with CDAD?

It tends to cause a very high white cell count ($> 15 \times 10^9/l$ common and $> 30 \times 10^9/l$ in 25% of patients), decreased serum albumin (very low levels seem to predict mortality) and altered electrolytes, notably hypokalaemia.

What are the markers of CDAD severity?

These include a very high white cell count ($> 15 \times 10^9/l$), hypoalbuminaemia, fever ($> 38.5°$), renal impairment and severe colitis.

How is CDAD treated?

Precipitating antibiotics should be stopped where possible. High-risk antibiotics for development of CDAD include levofloxacin and fluoroquinolones, second/third-generation cephalosporins, clindamycin and penicillins (especially amoxicillin/clavulanate). Anti-motility agents and laxatives should be avoided. Fluid and electrolyte balance correction is often needed. Surgery is occasionally needed, if toxic megacolon occurs.

Patients with diarrhoea and stool toxin positivity should be nursed in a side room; those without symptoms or who have not had symptoms in the past 48 hours need not be nursed in a side room nor treated with antibiotics. Proton pump inhibitors should be avoided where possible.

The first-line antibiotic is oral (or intravenous) metronidazole (400 mg t.d.s.), with a response rate of 75–98% and recurrence rate of 5–50%. Resistance is low. The second-line antibiotic is oral vancomycin 125 mg t.d.s.; larger doses are not superior, with a response rate of 80–97% and recurrence rate of 10–40%. This is not absolutely evidence based, as some evidence suggests equal efficacy overall of metronidazole and vancomycin, with response rates of around 92% each and relapse rates of around 16% each, but vancomycin is used with reservation because of the potential for resistant enterococci emerging. Relapse treatment is usually with metronidazole, and oral vancomycin is considered after two or more relapses. Other options include rifampicin, fusidic acid, teicoplanin and nitanoxanide. Recurrence is not usually because of resistance, and so the same treatment may be used as for the original episode.

Since stools may contain toxin for some time after resolution of symptoms, testing is not advised where symptoms have resolved.

Many measures for when antibiotics fail have observational but not rigorously evidence-based value; these include adjunctive probiotics, intravenous immunoglobulin and faecal donation per rectum or via a long jejunal line. Colectomy should be considered in patients with worsening blood markers since it is the only 'cure' and CDAD carries a huge mortality that is still underappreciated.

How is *C. difficule* controlled, especially in severe outbreaks?

Hygiene, isolation of symptomatic patients and antibiotic control are always important. Alcohol hand-rub does not kill spores, and so hand washing after seeing any patient with diarrhoea with soap and water after removal of apron and gloves is very important, for both staff and relatives. Dirty linen should be disposed of properly in sluices, and bins foot operated. Any new case of diarrhoea should be reported to the Infection Control Team, with all stool specimens from symptomatic patients submitted to microbiology. Visitors should be informed of any outbreak prior to visiting so they can make informed decisions on whether to visit. Affected wards should remain closed with closed doors. No patients should be discharged from the ward to anywhere other than to their own home, or moved around the hospital unless there is a clinical need. In severe outbreaks even more stringent measures are needed including the use of single-use patient washbowls, enhanced cleaning of isolation rooms and facilities (e.g. detergent clean, followed by bleach clean), and changing of curtains in bays. Strict antibiotic guidelines should be put in place, probiotics considered for all patients and, with growing evidence that proton pump inhibitors increase the risk of acquiring *C. difficile* two- to three-fold, the use of these drugs should be rationalised for all patients.

How is constipation managed?

After consideration and assessment for underlying causes, options include stimulants such as senna, softeners such as lactulose, and sodium docusate or Movicol. Fybogel is a bulking agent.

How is acute lower gastrointestinal bleeding (ALGIB) defined?

Haematochezia refers to bright-red or maroon blood per rectum. ALGIB is of recent onset (< 3 days), with bleeding beyond the ligament of Trietz, together with instability of vital signs or anaemia. Lower gastrointestinal bleeding (LGIB) constitutes around 20% of all gastrointestinal (GI) bleeding, more likely occurring in inpatients than as presentation to hospital, with a mean age of 66 years and an equal male–female ratio. It is mostly self-limiting, with an overall mortality of 2–4%.

What are the causes of LGIB?

These are listed in order of frequency in Box 2.13.

Which factors predict ongoing bleeding or death in ALGIB?

These are age > 60 years, haemodynamic disturbance, gross rectal bleeding, comorbidity and concurrent use of aspirin or non-steroidal anti-inflammatory drugs. Warfarin has little effect on outcome but does affect re-bleeding likelihood and need for transfusion.

Box 2.13 **Causes of lower gastrointestinal bleeding**

- Diverticular (usually acute, painless, mostly from left colon)
- Haemorrhoids
- Inflammatory bowel disease
- Infective
- Ischaemic colitis
- Polyp / post-polypectomy (up to 15 days post)
- Colorectal cancer
- Angiodysplasia (vascular ectasias occur anywhere, but predominantly caecal and ascending colon, often incidental, or present with haematochezia, melaena or iron deficiency anaemia)

How is ALGIB initially managed?

Coagulopathy should be corrected. Resuscitation should be with fluids, and blood if there is ongoing bleeding or severe anaemia to maintain a haemoglobin of around 10 g/dl. Those with ongoing or heavy bleeding, haemodynamic instability, a transfusion requirement of > 2 units or significant comorbidity should be managed in a high-dependency unit.

How is ALGIB investigated?

Radiological and endoscopic approaches may be considered.

Radiological

- Plain abdominal radiography is important prior to colonoscopy if bowel perforation or obstruction is suspected. Thumbprinting indicates transmural injury to the colon from ischaemic or infectious colitis. Double-contrast barium enema has no role in assessing ALIGB.
- Radionuclide scanning (technetium-99m red cell scintigraphy) has a smallish role but reasonable sensitivity and specificity for detecting active bleeding (at lower bleeding rates than that required for angiography) and reasonable localisation ability, although it cannot determine cause.
- Multidetector computed tomographic (CT) angiography can detect low bleeding rates, and can determine whether bleeding is active, identify the source and guide optimal treatment (colonoscopic intervention, angiographic embolisation, surgery). Limitations are that it can only identify active bleeding (so is not indicated for trivial or self-limited LGIB), risks contrast allergy and contrast-induced nephropathy (especially in diabetes or hypovolaemia) and has no therapeutic capability. Abdominal angiography also risks contrast and other complications and is less commonly used.

Endoscopic

- Oesophagoduodenogastroscopy is important in severe haematochezia because around 15% of patients with severe haematochezia have an upper GI source of bleeding.
- Flexible sigmoidoscopy after phosphate enema or urgent (within 24 hours) colonoscopy following full bowel cleansing has a very high diagnostic yield. There may be a role for emergency colonoscopy (within 12 hours) for massive diverticular haemorrhage, although greater consensus is to stabilise the patient first.
- Wireless or video capsule endoscopy (entire small bowel visualisation) or enteroscopy (evaluation of

proximal 60 cm of jejunum) may be considered if no source is found.

How is ALGIB treated?

The three main treatment modalities are colonoscopic, interventional radiological/angiographic embolisation and surgery. There is no role for medical treatments if bleeding. Surgery is needed in up to 25% of patients requiring blood transfusion and is indicated for where a bleeding source has been identified but other treatments have failed, fulminant bleeding or recurrent bleeding without localisation. Directed segmental resection is considered rather than blind segmental colectomy.

What do you know about the molecular basis and genetics of CRC risk?

More than 70% of CRCs develop from sporadic adenomatous polyps. The most common well-defined hereditary syndromes are the familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC)/ Lynch syndromes. Peutz Jeghers syndrome is rare.

FAP is an autosomal dominant disorder in which there is a germline mutation in the tumour suppressor gene for adenomatous polyposis coli (*APC*) on chromosome 5. It accounts for < 1% of all CRCs. Patients often have hundreds of pedunculated colonic polyps. Extracolonic manifestations may occur (previously referred to as Gardner and Turcot syndromes), including duodenal adenomas and cerebral and thyroid tumours. In HNPCC there are germline mutations in DNA mismatch repair genes giving rise to pedunculated and flat polyps, predominantly in the proximal colon.

The proportion of CRCs attributable to HNPCC is unclear, but HNPCC probably accounts for a significantly higher proportion than FAP. Associations include endometrial, ovarian, gastric and other cancers.

Clusters of CRCs also occur in some families without a recognisable syndrome, suggesting a genetic origin. The immediate family members of a patient with CRC have a two- to three-fold relative risk of developing the disease.

Ulcerative colitis is unequivocally associated with increased CRC risk, high-risk factors including disease > 10 years, extensive disease and the presence of primary sclerosing cholangitis.

Factors which may promote the adenoma to CRC sequence include *APC* gene mutations, k-*ras* mutations, deleted in colon cancer (*DCC*) mutations, and *p53* gene mutations.

Which factors determine a higher risk of malignant transformation within a polyp?

These include large size, a sessile or flattened appearance, severe dysplasia or squamous metaplasia, villous rather than tubular architecture and multiplicity (e.g. FAP).

How is CRC staged?

There are four stages:

- Stage I (Dukes' A) – primary tumour into but not through muscularis propria, and no metastases
- Stage II (Dukes' B) – primary tumour grown through to serosa and peritoneal surface but no metastases
- Stage III (Dukes' C) – any size of primary tumour with lymph node metastases
- Stage IV – presence of distant metastatic disease.

How is CRC managed?

CRC is a curable disease with over 90% of patients alive at 5 years after surgical removal of a Dukes' A lesion. Despite this, it remains the second most common cause of cancer death in the UK. Important associations of CRC with diet, obesity and exercise suggest prevention is often possible, and screening is considered for those with HNPCC, FAP and others at high risk.

The 2-week wait system is important for those with symptoms. A total of 35 000 people develop CRC each year in the UK, most sporadic. Most affect the rectum or rectosigmoid and may present with rectal bleeding or an increase in stool frequency; right-sided cancers are more likely to be detected through anaemia. Colonoscopy is the standard investigation, but flexible sigmoidoscopy followed by barium enema, or CT scanning, are alternatives in patients with major comorbidity. If CRC is confirmed, staging involves CT imaging of chest, abdomen and pelvis, but for rectal cancers magnetic resonance imaging gives better information about local pelvic disease burden and nodal status and helps inform decisions about pre-operative chemotherapy. All CRCs should be discussed at multidisciplinary meetings to decide the optimum treatment strategy.

As well as traditional surgical approaches, rectal cancer has seen a variety of new surgical approaches, minimally invasive procedures are on the increase, and multimodal treatments include radiotherapy before surgery for tumours at moderate risk of recurrence and chemoradiotherapy for tumours at high risk of recurrence. Adjuvant chemotherapy may be considered for a stage I CRC after excision, depending upon pathological type, imaging results and any previous treatments. Chemotherapy is standard for patients with stage II CRC or rectal cancer and high risk of recurrence or stage III CRC or rectal cancer. Chemotherapy and biological therapies include folinic acid plus fluorouracil, and capecitabine plus oxaliplatin. Colonic stents may help acute large bowel obstruction.

What do you know about CRC screening?

CRC is a major public health challenge. Outcome is directly related to histological staging and patients with Dukes' A lesions have a 5-year survival of up to 90%. Early detection is imperative, and this includes prompt investigation of patients with symptoms, selective screening of high-risk patients and population screening.

Patients at increased risk of CRC should be considered for surveillance. This group includes patients with a positive family history and patients with long-standing inflammatory bowel disease. The lifetime risk of CRC is 1 : 50, rising to 1 : 17 if one first-degree relative is affected and > 1 : 10 if two or more first-degree relatives are affected. Patients with a family history of CRC should be offered screening if one first-degree relative is affected under 45 years of age or if two first-degree relatives have been affected at any age. Screening should be by colonoscopy at presentation or at age 35–40 years, whichever is later. If negative, further colonoscopy is advised at 55 years. For people with more than two affected first-degree relatives a clinical geneticist should be consulted because of the possibility of FAP or HNPCC, and those with a known family history of such a genetic syndrome as HNPCC should be screened.

The arguments for a national screening programme are that CRC is common, with a known premalignant lesion (adenoma). As it takes a long time (years) for adenomas to undergo malignant change, intervention is likely to significantly reduce the morbidity and mortality burden of CRC. The two problems faced by population screening are which patients to target and by which method:

- Faecal occult blood testing is non-invasive, cheap and simple and currently used. It is relatively insensitive and non-specific, but has the potential to save many lives at an acceptable cost, reducing CRC mortality by 15–33%.
- Flexible sigmoidoscopy detects up to 80% of CRCs as it examines the entire left colon and rectum, although even when combined with faecal occult blood testing this combined strategy misses 24% of CRCs. It is likely to be introduced for those aged 55, with colonoscopy reserved for those in whom a polyp is found.
- Colonoscopy is the gold standard diagnostic test.

Cardiovascular problems

CASE 2.7 WEIGHT GAIN, OBESITY, AND PREVENTION OF CARDIOVASCULAR DISEASE

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Charlotte Holmes, aged 38 years
>
> Thank you for seeing this lady, who is seeking a specialist opinion about her weight. She has a body mass index of 32 kg/m^2 and a strong family history of obesity and type 2 diabetes. She has a random blood glucose of 10.9 mmol/l and a blood pressure of 160/90. Her total cholesterol is 5.6 mmol/l. Her thyroid function is normal. I recently commenced ramipril and have asked the dietitian to review her diet.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Charlotte Holmes is a 38-year-old nurse who has problems with her weight. She has always tended to be overweight but despite dietary advice has put on approximately 5 kg over the past year. Her current body mass index (BMI) is 32 kg/m^2. She is increasingly shy about undressing and no longer goes swimming or to the gym. Her occupation is stressful but does not lend itself to fitness. She suffers from chronic back pain, and has had other complications probably related to her weight, including gallstones and a deep vein thrombosis in pregnancy. She has impaired fasting glucose. She has a strong family history of type 2 diabetes and her mother died at the age of 56 from a myocardial infarction. She is a non-smoker. She has slightly erratic menstrual periods but is otherwise well. She has resigned herself to not ever being 'thin' but is desperately keen to ensure that no secondary cause is being missed, to lose some weight, and to optimise primary prevention of cardiovascular disease (CVD) as she wants to 'see her two children grow up'.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Consider causes.** Obesity develops when energy intake exceeds expenditure over a long period, and weight gain and obesity largely result from eating too much and not taking enough exercise. The processes regulating energy balance are tightly regulated but mechanisms of appetite control are easily overwhelmed by a willingness to eat when not hungry. Control pathways include:

- Short-term signalling of hunger and satiety with hormones derived from the gastrointestinal tract to the central nervous system
- Long-term signalling of energy stores via the hormone leptin and insulin to the brain; leptin is a satiety hormone produced in adipose tissue which stimulates the hypothalamus to produce anorexogenic hormones that decrease appetite and fat mass and interact with various other systems, including the sympathetic nervous system, the thyroid and the gonadal axis
- Control of metabolism.

Rare genetic syndromes that present in early childhood with severe obesity include leptin deficiency and mutations in the pro-opiomelanocortin gene. Gene defects such as the *OB4* defect impair leptin synthesis, but intriguingly therapeutic leptin has failed as an elixir for weight loss. Other peptides including ghrelin, adiponectin and resistin have not fully understood complex roles in weight homeostasis.

Most obesity develops as a result of modern lifestyles in genetically susceptible individuals. These changes include increased consumption of high-energy food and at the same time physical activity levels have declined dramatically, the nefarious edge of a double-edged sword that brings safer, easier lives, and television and computers make a significant contribution. In many societies less affluent people appear to be at greater risk. Around 90% of Western people are predisposed to developing the 'abdominal' phenotype. We put on 0.9 g every day from around ages 25 to 55, which contrasts with 'wild-type' humans, who no longer exist, but whose weight plateaued in adulthood. We are, on average, 15 kg heavier than 100 years ago (although a little taller, by approximately 1 cm/decade). Between 13% and 14% of the UK population is obese, and over 20% of the US population have incipient 'diabesity'. 'Cocacolarisation' is very evident in communities recently exposed to Western lifestyles, as exemplified by Aboriginals where the 'thrifty gene' hypothesis has been postulated – that our ancestors were predisposed to diabetes because those predisposing mechanisms allowed survival during famine. But perhaps in reality, all people have this 'thrifty' potential.

Secondary causes of obesity are listed in Box 2.14.

Box 2.14 **Secondary causes of obesity**

- Hypothyroidism
- Cushing's syndrome
- Polycystic ovarian syndrome
- Insulinoma
- Hypothalamic or pituitary disease
- Drugs
- Genetic syndromes, e.g. Laurence–Moon–Biedl syndrome
- Leptin deficiency or leptin receptor defects

■ **Consider consequences.** Obesity is a worldwide epidemic and one of the most important global public health issues and preventable causes of disease and mortality. The prevalence has risen dramatically in a single generation, with some of the most rapid increases occurring in developing countries, at high personal, health-care and society cost. An ever-increasing range of diseases and health problems has been linked to obesity. In 2004, increased BMI alone was estimated to account for 2.8 million deaths, while the combined total with physical inactivity was 6.0 million, surpassing the excess mortality associated with tobacco and approaching that of high blood pressure, the top risk factor for death. There is a strong link between type 2 diabetes and obesity – a 25% increase in risk for every 1 kg/m^2 increase in BMI above 22. Consequences of weight gain and obesity are outlined in Box 2.15.

Box 2.15 **Consequences of obesity**

- Low self-esteem and depression
- Discrimination
- Type 2 diabetes
- Cardiovascular disease – heart failure, hypertension and coronary heart disease
- Worsening of chronic obstructive pulmonary disease and asthma
- Obstructive sleep apnoea
- Symptoms of breathlessness in asthma and other lung disease
- Venous thromboembolism
- Non-alcoholic fatty liver disease, and transition to non-alcoholic steatohepatosis (threatens to become the leading cause of cirrhosis and hepatocellular carcinoma)
- Biliary disease
- Intertrigo
- Soft-tissue infection
- Varicose veins
- Back pain
- Osteoarthritis
- Hepatic steatosis (fatty liver)
- Increased risk of falls
- Stress incontinence
- Oligomenorrhoea and infertility
- Risks from the contraceptive pill
- Pregnancy complications
- Anaesthetic risks
- Increased risk of some cancers (now strong evidence for strong association)

Patient perspective

The effects on self-esteem should not be underestimated. Expectations should not be destroyed. Rather than focusing on past 'failure' to lose weight, focus on what can be done:

- A short list of tests to exclude secondary causes and build in reassurance
- Referral to a dietitian
- Gradual but sustained weight loss through adjustments in diet and exercise routines (see Summary box)
- Reassurance that such measures can halt the development of diabetes
- Consideration of anti-obesity drugs if necessary
- Exploration of possible depression and consideration of treatment.

Past medical history

All of her past medical problems could be explained by obesity.

Drug and allergy history

Drugs commonly provoking weight gain include corticosteroids, antithyroid drugs, sulphonylureas and antipsychotics.

Family history

A family history of obesity is often present.

Social history

Explore fully what she eats, and physical exercise undertaken.

SUMMARY BOX – ASSESSMENT AND PLAN

The following are important to establish – weight and height to derive the body mass index (BMI), waist circumference, blood pressure, urinalysis for glycosuria, thyroid function, lipid profile, fasting plasma glucose.

BODY MASS INDEX (kg/m^2)

< 18.5 = underweight
18.5–24.9 = normal range
25–29.9 = overweight/pre-obese
≥ 30 = obese

- Other hormonal tests (e.g. for polycystic ovarian syndrome) are usually directed by the history, but only a very small proportion of people have a secondary cause.
- A dietitian should be consulted.
- Weight loss of 0.5–1 kg/week is an ideal, but frequently not attainable, goal.
- She should be advised to avoid food with more than 2–3 g fat/100 g.
- Exercise such as brisk walking, swimming or cycling is recommended for 30–40 minutes a day on at least 5 days of the week.
- Drug therapy is considered only as an adjunct for patients with a BMI over 30 when other measures have failed.
- Surgery, for example gastric stapling, may be considered for patients with very high BMIs.

Box 2.16 **Clinical diagnosis of metabolic syndrome**

National Cholesterol Education Program

- Central obesity: waist circumference ≥ 88 cm/36 inches (women) and ≥ 102 cm/40 inches (men)
- Blood pressure ≥ 130 mmHg/≥ 85 mmHg
- Fasting glucose ≥ 6.1 mmol/l
- Serum triglycerides ≥ 1.7 mmol/l
- High-density lipoprotein cholesterol < 1.3 mmol/l (women) and < 1.0 mmol/l (men)

International Diabetes Federation

- The criteria are similar, but central obesity can be assumed and waist circumference does not need to be measured if body mass index is > 30 kg/m^2. Additionally required are any two of the lipid (or on lipid treatment for) or blood pressure features above or raised fasting glucose > 5.6 mmol/l or previously diagnosed type 2 diabetes.

Discussion

What do you know about abdominal obesity and the hypertriglyceridaemic phenotype and the metabolic syndrome?

Abdominal obesity, which is closely associated with intra-abdominal or visceral fat (which can be distinguished from subcutaneous fat by imaging) and measured by waist circumference (male > 102 cm, female > 88 cm) or waist–hip ratio, predicts coronary disease better than the BMI. Furthermore, abdominal obesity is associated with insulin resistance and predicts the development of type 2 diabetes. High waist and fasting triglyceride measurements – the hypertriglyceridaemic waist – are markers for the metabolic syndrome. There are numerous defining criteria (Box 2.16) for the metabolic syndrome, notably those set out by the International Diabetes Federation and the revised National Cholesterol Education Program.

Homeostasis refers to constancy of the internal environment (negative feedback). Allostasis refers to adaptation of the internal environment to changing conditions (positive feedback). This is the problem with obesity. It engenders the nasty cascade of insulin resistance, hyperinsulinaemia, hypertension, hyperglycaemia, dyslipidaemia and vascular disease and the trouble is that it is too late to treat the end stage, which is when we see it in outpatient clinics and hospitals. Type 1 diabetes, characterised by loss of beta cell function and endogenous insulin production, carries a two- to three-fold increase in risk of developing CVD, notably increased if there is diabetic nephropathy. Type 2 diabetes, characterised by insulin resistance and eventual beta cell failure, often occurs in the context of the metabolic syndrome and all patients are at increased risk of CVD, even in the absence of nephropathy. The metabolic syndrome is highly prevalent among individuals with partial lipodystrophy and spinal cord injury, suggesting that lack of subcutaneous adipose tissue and muscle atrophy play critical roles in metabolic disturbances. Sleep disorders may cause metabolic disturbances by inducing neurohumoral changes and perhaps altered muscle fibre adaptation. Reducing weight by 5–10 kg, by diet and exercise or by anti-obesity drugs, reduces CVD risk substantially and reduces diabetes risk by over 50%. Some newer anti-diabetic agents improve insulin resistance, and reduce lipids and weight, and could potentially be used to treat metabolic syndrome.

How is obesity managed?

Modern weight management incorporates optimisation of health and risk factors, short-term weight loss, and long-term weight maintenance and prevention of regain. People in need of professional weight management involving a structured programme addressing diet and physical activity, and behavioural management, can be identified by a large waist (> 102 cm for men, > 88 cm for women), which can be cost effective in generating 5–10% weight loss in 30–40% of patients. The available anti-obesity drugs (orlistat) and liraglutide (for obese patients with diabetes) can double the weight loss and clinical benefits for some years. Very-low-energy diets (400–800 kcal) produce 10–20 kg weight loss that can be maintained using stepped food reintroduction and anti-obesity drugs. For most overweight and obese patients, a modest weight loss of 5–10 kg, achievable by many methods, brings multiple benefits. A target loss of 15 kg is necessary to reverse the diagnosis of type 2 diabetes, and restore a non-diabetic life expectancy. Bariatric surgery is effective and improves multiple health risks for extreme obesity (BMI > 40) and when severe medical complications (e.g. diabetes, sleep apnoea) are present. Surgery can help committed patients achieve weight loss and health benefits, but it requires the support of a multi-disciplinary team including dietitians. Procedures include those that restrict the amount of food that can be eaten, or those that cause malabsorption of calories, or combinations of these. Adjustable gastric banding and gastric bypass are the commonest procedures.

What do you understand by total cardiovascular risk assessment?

CVD due to atherosclerosis is the foremost cause of premature mortality and of disability-adjusted life years in Europe, and increasingly common in developing countries. The causes of CVDs are multifactorial. Some risk factors relate to lifestyle, such as tobacco smoking, lack of physical activity and dietary habits, and are thus modifiable. Other risk factors are also modifiable, such as elevated blood pressure, type 2 diabetes and dyslipidaemias, or non-modifiable, such as age and male gender. The Joint British Societies' – British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society and the Stroke Association – guidelines on prevention of CVD promote a consistent multidisciplinary approach to managing established atherosclerotic CVD and those at high risk of developing symptomatic atherosclerotic disease. The objectives are to reduce the risk of a non-fatal or fatal atherosclerotic cardiovascular event, including the need for a revascularisation procedure in any artery territory, and to improve quality and length of life.

Total CVD risk versus single risk factors

The concept of medical intervention based on estimated total CVD risk in asymptomatic people is widely accepted because CVD is multifactorial, risk factors tend to cluster and co-existent risk factors have a multiplicative effect on CVD risk. There are exceptions, e.g. when blood pressure is particularly high treatment is required regardless of total CVD risk. Potential disadvantages of estimating total risk are that treatments will tend to focus on older people, in whom CVD risk is usually ≥ 20%, especially for men. Younger people will always be at low total CVD risk over the short term, although they may be at relatively high risk relative to peers of the same age. Considering only short-term CVD risk for younger people ignores potential life-years to be gained by treating someone earlier when they are on track to become high risk later in life. Younger people with adverse risk profiles will have a higher CVD risk than predicted because blood pressure, total cholesterol (TC) and glucose all rise, and high-density lipoprotein cholesterol (HDL-C) falls, with age. The charts are for three age ranges: < 50, 50–59, ≥ 60 years; however, risks for these are based on ages 49, 59 and 69 respectively. Thus, in the lower two bands, except for those aged 49 and 59, risk will be overestimated, and in the upper band risk will be overestimated for those aged under 69 and underestimated for those aged 70 or over. So projecting CVD risk to 49 years in younger people projects intervention to those at higher risk in this younger age group, while a decision to intervene in older persons requires individual judgement.

CVD risk assessment systems

Most guidelines on CVD prevention use risk assessment systems based on either Framingham (US) or SCORE (European) data. European guidelines recommend the SCORE system because it is based on large cohorts, whilst UK guidelines prefer Framingham data, since the SCORE data only predict fatal CVD, which underestimates the true burden of total CVD based on non-fatal and fatal CVD events.

Those who should have CVD risk assessment

All adults aged 40–80 years without a history of CVD or diabetes or not already on treatment for blood pressure or lipids or not in the list in Box 2.17 (all of whom should receive professional intervention to achieve targets) should be considered for an opportunistic comprehensive risk assessment in primary care. Younger adults with a family history of premature CVD should also be assessed, arbitrarily defined in relation to coronary heart disease (CHD) in a male first-degree relative < 55 years or a female first-degree relative < 65 years. Women are at equal risk of CVD as men; it simply tends to present later.

Box 2.17 **People at high cardiovascular disease (CVD) risk (thresholds for treatment)**

1. People with established atherosclerotic CVD
2. Asymptomatic, apparently healthy individuals without established CVD who have a combination of risk factors which puts them at high total risk (estimated multifactorial CVD risk ≥ 20% over 10 years) of developing symptomatic atherosclerotic CVD
3. People with diabetes mellitus (type 1 or 2)

In addition, other people with particularly elevated single risk factors also need CVD prevention because they are at high CVD risk regardless of other risk factors: elevated blood pressure ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic, or lesser degrees with target organ damage – retinopathy, micro/macroalbuminuria, raised creatinine, left ventricular hypertrophy; elevated total cholesterol to high-density lipoprotein cholesterol ratio ≥ 6.0; renal disease; familial dyslipidaemia.

Box 2.18 **Five risk factors and total risk prediction**

1. Age (< 50, 50–59, ≥ 60 years)
2. Sex
3. Smoking habit history
4. Systolic blood pressure
5. The total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio (HDL-C assumed to be 1.0 if unavailable)

The estimated probability (percentage chance) of developing cardiovascular disease (CVD) over 10 years is referred to as total CVD risk, synonymous with the epidemiological term absolute risk; a total CVD risk ≥ 20% over 10 years is defined as high risk, implying that at least 20 in 100 people with the same risk factors would be expected to develop CVD over the next 10 years.

Risk assessment

CVD risk refers to a combined endpoint of CHD (fatal and non-fatal myocardial infarction and new angina) plus stroke (fatal and non-fatal stroke and cerebral haemorrhage) and transient cerebral ischaemia. Some primary cardiovascular events such as aortic aneurysm and lower limb ischaemia are not included, but are a small proportion of all CVD events. The stroke endpoint is based on occlusive cerebral infarction (related to blood pressure and lipids) and intracerebral haemorrhage (related to blood pressure). Prediction charts estimate the total risk of an asymptomatic individual of developing CVD based on five risk factors (Box 2.18).

In the charts, CVD risks of ≥ 10%, ≥ 20% and ≥ 30% are highlighted. Those at highest risk are thus identified and management of blood pressure and lipids is addressed in this overall context such that, for example, the same TC value might qualify for treatment in one individual but not another. Risk factors not included in the CVD risk prediction charts should be considered in assessing and managing a person's overall CVD risk: younger adults with a family history of premature CVD; obesity (BMI ≥ 30 kg/m^2) and especially central/abdominal obesity; low HDL-C (< 1.0 mmol/l in men and < 1.2 mmol/l in women); raised fasting triglycerides (≥ 1.7 mmol/l); impaired glucose regulation; premature menopause. Risk assessment should be repeated within 5 years in people not found to be at high risk.

Risk assessment for those already on treatment for blood pressure or lipids

Estimating risk is more complicated and on-treatment values tend to underestimate risk. Attempts to do so should be based on pre-treatment values or, if unavailable, these people should be assumed to be at high risk rendering risk assessment unnecessary.

Groups prioritised for CVD prevention

CVD prevention should focus equally on those groups listed in Box 2.17.

National Institute for Health and Clinical Excellence (NICE) guidance

NICE guidance on lipid management endorses the Joint British Societies (JBS2) recommendations in advocating a CVD risk threshold of 20% over the next 10 years as an indication for statin therapy. However, NICE proposes that the upper age limit at which CVD risk is estimated is extended to 75 years rather than 70 years, but there has been no readily available means of assessing risk in older people. Revised charts now address this. NICE also lays more emphasis on an adverse family history of CVD.

What are the lifestyle interventions and targets in people with high CVD risk?

Lifestyle targets for all people (not just high CVD risk) are outlined in Box 2.19.

Saturated fat is positively associated with CVD. Polyunsaturated fatty acids of n-6 and n-3 classes are inversely proportional to risk. Linoleic acid is the main n-6, found mainly in vegetable oils. Alpha-linoleic acid is a precursor of the n-3 group, its main source being certain vegetable oils – soybean, safflower, linseed oils. Plant stenols or sterols may be beneficial. People who regularly eat fish have a lower risk of fatal CHD, including sudden death. A Mediterranean diet is recommended, inclusive of oily fish, but there is no evidence for supplementation of beta-carotene, antioxidants, vitamins C or E or folic acid. Energy intake and expenditure balance must be adjusted to achieve a normal BMI. In clinical practice, however, realistic and individual targets should be set for weight loss. With an exercise programme, weight loss of 1–2 kg/month can be achieved by reducing the caloric intake by less than 500 kcal/day below that required for weight maintenance. Caloric intake is most efficiently reduced by reducing the consumption of high-energy-dense foods, especially saturated fats, refined carbohydrates and some alcoholic drinks, and for obese people it is necessary to restrict calories as well. Fat intake should

Box 2.19 **Lifestyle targets in all people (not just high cardiovascular disease risk)**

- Do not smoke
- Maintain ideal body weight (body mass index approximately 20–25 kg/m^2) and avoid central obesity
- Keep dietary intake of fat to ≤ 30% of total energy intake
- Keep saturated fats to a minimum (≤ 10% of total fat intake)
- Keep intake of dietary cholesterol to < 300 mg/day
- Replace saturated fats with monounsaturated fats
- Increase fruit and vegetable intake to at least five portions per day, and encourage nuts and legumes
- Aim for a regular intake of fish and other sources of n-3 fatty acids (at least two servings of fish per week or 70 g; tablets may be considered in those not achieving this following myocardial infarction)
- Limit alcohol to < 21 units/week for men and < 14 units per week for women
- Limit salt intake to < 100 mmol/l per day (< 6 g sodium chloride or < 2.4 g sodium per day)
- Aim for regular aerobic physical activity of at least 30 minutes per day, most days of the week, e.g. brisk walking, swimming, cycling and encouraging exercise into the daily routine (e.g. use of stairs)

be less than 30% of total intake. Foods with high fat content should be replaced with vegetables, fruit and cereal products. Increasing physical activity can make an important contribution to weight loss, in preserving a stable weight and in preventing weight gain. Most people begin to gain weight again a few months afterwards, and motivation is needed! Although a study confirmed that 30 minutes of moderate-intensity exercise on most days was associated with a reduction in blood pressure and TC and triglyceride levels, 60–75 minutes was required to reduce weight, waist circumference, fasting glucose and low-density lipoprotein cholesterol (LDL-C), increase HDL-C and reduce overall CVD risk. In short, we need to 'move a little more and eat a little less'.

Is unaccustomed exercise risky?

Platelet activation during unaccustomed exercise causes a 50-fold increase in the risk of sudden death and a 100-fold increase in the risk of acute myocardial infarction.

What are the blood pressure targets in people with high CVD risk?

Targets for blood pressure are given in Case 2.14 (Hypertension), and may be more rigorous in selected high-risk people. Lowering systolic or diastolic blood pressure by 10 mmHg or 5 mmHg, respectively, reduces the risk of CHD by about 25% at age 65.

What are the lipid targets in people with high CVD risk?

Targets for lipids are given in Case 2.13 (Dyslipidaemia).

What are the blood glucose targets in people with high CVD risk?

Glycaemia is continuously related to the risk of developing CVD. In all high-risk people the optimal fasting plasma glucose is ≤ 6.0 mmol/l and glycated haemoglobin (HbA_{1c}) ≤ 6.1%. In diabetes the optimal targets are 4.0–6.0 mmol/l for fasting or pre-prandial glucose and ≤ 6.5% for HbA_{1c}.

Can type 2 diabetes be prevented?

Impaired glucose regulation is associated with increased risk of developing diabetes and death from atherosclerotic CVD and all causes. Progression to diabetes can be prevented or postponed by lifestyle intervention. Other measures that thwart progression include acarbose in impaired glucose tolerance and orlistat in obese people with normal or impaired glucose tolerance.

Why might older patients be at increased risk of CVD?

As well as the higher prevalence of atherosclerosis, ageing is associated with pro-inflammatory (increase in inflammatory markers, e.g. C-reactive protein, interleukin-6) and prothrombotic (increase in fibrinogen, clotting factors and D-dimer) tendencies.

Outline the place of angiotensin-converting enzyme (ACE) inhibitors in CVD

ACE inhibitors have had proven benefit in heart failure for many years, and left ventricular dysfunction following myocardial infarction. The vasodilatory and haemodynamic effects (which help prevent remodelling following myocardial infarction, for example) may not be the only benefits. ACE inhibitors may also improve endothelial structure and function with beneficial effects on cytokine profiles, inflammation and oxidative stress, with reduced proliferation of vascular smooth muscle cells, lower risk of plaque rupture and enhanced fibrinolysis.

ACE inhibitors in heart failure are discussed in Case 2.10. ACE inhibitors in hypertension are discussed in Case 2.14. They may be especially beneficial in younger patients whose hypertension tends to have a high renin–angiotensin–aldosterone drive. There were 3577 patients with diabetes in the HOPE study and the improvements in microvascular outcomes were consistent with other evidence that ACE inhibitors reduce diabetic nephropathy in type 1 and type 2 diabetes and retinopathy in type 1 diabetes. EUROPA showed similar benefits in diabetes. The benefits of ACE inhibitors in secondary stroke prevention were shown in the PROGRESS study. In view of beneficial results in a range of high-risk patients (including those with heart failure, myocardial infarction, hypertension, diabetes, stroke), the EUROPA trial examined people with stable coronary artery disease otherwise considered to be at low risk and without heart failure. It showed gradual onset and progressive benefit of ACE inhibitors (reduction in cardiovascular death, myocardial infarction or cardiac arrest by 20%), consistent with the ramipril HOPE study, establishing antiatherosclerotic as well as antihypertensive properties of perindopril.

Can these benefits of ACE inhibitors in CVD be extrapolated to angiotensin receptor blockers (ARBs)?

The place of ARBs in heart failure and hypertension is discussed in Cases 2.10 and 2.14, respectively. The valsartan antihypertensive long-term use evaluation (VALUE) trial looked at reducing blood pressure in high-risk patients. Valsartan produced a statistically significant increase in myocardial infarction and stroke compared with amlodipine and raised concerns that ARBs might be neutral or even harmful on myocardial infarction rates despite a reduction in blood pressure. Furthermore, the CHARM-alternative heart failure trial showed an increase in myocardial infarction with candesartan, the study on cognition and prognosis in the elderly (SCOPE) a non-significant increase and the LIFE study no protection against myocardial infarction despite blood pressure benefits. However, to infer that these drugs may be harmful may be incorrect. In the absence of a placebo in VALUE, it was not possible to say if amlodipine was better or valsartan worse; both drugs could be protective. Other large trials such as OPTIMAAL and VALIANT in patients post myocardial infarction or with heart failure did not show excessive cardiovascular events and a systematic review did not show statistically increased cardiovascular risk with ARBs. And in ONTARGET (25 620 patients), telmisartan was as protective as ramipril (HOPE study) alongside other standard treatments in reducing cardiovascular death, myocardial infarction, stroke, and hospitalisation for heart failure in a broad range of high-risk patients and with better tolerability.

Have you heard of the 'polypill' and mass population preventive strategies?

This combination of three low-dose antihypertensives, a statin, aspirin and folic acid, advocated for all (without contraindications) over the age of 55, all with diabetes over the age of 35 and all with known CVD, could reduce the risk of CVD events by over 80%. It is not a substitute for lifestyle measures.

An important role of epidemiology is in preventing premature deaths, most of which occur in 'middle age', arbitrarily defined by some as age 35–69. Worldwide there are around 60 million deaths and 130 million births yearly, and epidemiologists predict that of those 130 million around 20 million will die aged 0–34 (largely preventable), 40 million aged 35–69 and 70 million aged 70 and above. The big four killers that are increasing in prevalence are human immunodeficiency virus infection, smoking (especially in China), alcohol (especially in Russia) and obesity with its associated vascular risks (especially in the West). Smoking triples the risk. A 20 mmHg increase in blood pressure doubles risk. Dyslipidaemia is deadly, and a 2 mmol/l reduction in LDL-C reduces risk by 40%. And obesity is the non-smoking epidemic, although it still kills less people than smoking. In terms of secondary prophylaxis, risk is reduced three-fold by combined statin therapy, antihypertensive therapy and aspirin. A 50% risk of death from recurrence in 10 years is reduced by half to one-sixth with treatment, and many would argue that we do not test platelet function before using aspirin, yet spend considerable time investigating blood pressure and cholesterol, yet treatment remains underdone. Of course the strong arguments against such a liberal attitude to prescribing are that it deflects from lifestyle measures and that drugs can of course be harmful (though many would argue that premature death is serious whereas taking a pill is relatively less so!). In terms of primary prevention, avoidance of tobacco and adiposity are key, and since the 1950s deaths in middle age have halved, and vascular deaths fallen four-fold, largely attributable to anti-smoking advice. In the 1950s, 50% of strokes occurred in middle age, and now that figure is less than 1%, although this trend began before instigating evidence-based treatments.

CASE 2.8 CHEST PAIN AND STABLE ANGINA

Candidate instructions

Role

You are a doctor in a rapid access chest pain clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr John Aubrey, aged 49 years
>
> Thank you for seeing Mr Aubrey, who has type 2 diabetes, used to smoke and has a family history of ischaemic heart disease. His blood pressure is 160/94. His TC:HDL ratio is > 6 mmol/l. He reports recent worsening episodes of chest pain that I suspect are angina and I would appreciate your urgent investigation.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr John Aubrey is a 49-year-old man who has had chest pains of increasing frequency and severity over the last month. Pains are central and crushing in nature, and have increased in frequency from once or twice a week to almost every day. They always occur on exertion but recently have been provoked by minimal activity such as walking up a few stairs at home. He has a history of diet-controlled diabetes, high cholesterol and high blood pressure, and currently takes aspirin 75 mg, simvastatin 40 mg, perindopril 4 mg and atenolol 50 mg, all daily. He has a sedentary occupation as a cinema projectionist. He lives with his wife and two children, and has not smoked for 20 years. His mother died of a heart attack aged 62 and his father from a stroke aged 78. He is not very concerned about these pains, believing them to be indigestion, as they often seem to come on when he gets up and walks around after a heavy meal.

How to approach the case

Data gathering in the interview and interpretation and use of data gathered

Presenting problem(s) and symptom exploration

■ **Elicit details of chest pain.** Elicit the features listed in Table 2.15 that might suggest cardiac ischaemia.

Ask about rest pain and nocturnal pain.

■ **Ask about associated symptoms.** Ask about dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and ankle swelling. Syncope or presyncopal symptoms are unusual, but could represent aortic stenosis or non-sustained arrhythmias or conduction block.

■ **Explore risk factors.** Most important is the likelihood of the patient having the underlying pathology of coronary artery disease (CAD). Risk factors include:

- Family history (especially at an early age)
- Smoking (including passive)
- Hypertension
- Dyslipidaemia
- Diabetes
- Obesity
- Sedentary lifestyle
- Inflammation (e.g. rheumatoid arthritis)
- Risk much higher if renal disease, peripheral vascular disease, cerebrovascular disease
- Psychosocial.

Numerous studies have linked infections to CAD (e.g. *Chlamydia pneumoniae*). It is likely that these are not causative, but that the total burden of infection at various sites from various organisms may influence progression of atherosclerosis.

■ **Consider the severity of angina.** If angina seems likely, consider its severity (Box 2.20).

■ **Consider the differential diagnosis of chest pain.** This includes dissecting aortic aneurysm (classically radiating to the back), pulmonary embolus/pleuritic irritation, pericarditis, pneumonia, dyspepsia, cholecystitis, shingles/radicular pain and musculoskeletal pain (including viral disease and costochondritis).

Patient perspective

New angina is often perceived by patients to be 'indigestion', especially if induced by meals.

Past medical history

He has the typical constellation of risk factors for ischaemic cardiac pain.

Drug and allergy history

He is taking appropriate drug therapy to modify cardiovascular disease (CVD) risk, but this could be enhanced if unstable angina seems likely, and urgent assessment may well include coronary angiography.

Family history

Family history is very relevant in CVD.

Table 2.15 Details of chest pain suggesting cardiac ischaemia

	Suggest cardiac ischaemia
Site	Poorly localised retrosternal discomfort
Character	Often described as heavy, pressing, dull, tight or band-like Often patients deny pain and refer to it as 'just a discomfort'
Radiation	May radiate to arms, neck, jaw, gums or abdomen (sometimes these may be the only sites)
Onset	Builds up over minutes
Duration	Episodic rather than constant (reproducibility a key discriminating factor) Duration of recovery is a key discriminating feature of angina (> 30 minutes unlikely to be angina)
Precipitating / exacerbating factors	Exertion, especially walking uphill Cold (a key discriminating factor) Food (a key discriminating factor)
Relieving factors	Rest Nitrate spray Not relieved by posture or movement

Box 2.20 **Canadian Cardiovascular Society classification of angina**

1. Angina only on strenuous, rapid or prolonged exercise
2. Slight limitation of ordinary activity (e.g. angina on rapidly climbing stairs or walking uphill)
3. Marked limitation of ordinary activity
4. Inability to carry out physical activity without discomfort (includes unstable angina)

Social history

The sedentary lifestyle is a risk factor.

SUMMARY BOX – ASSESSMENT AND PLAN

- He probably has ischaemic cardiac pain, and the rapid evolution and minimal provocation suggest unstable coronary anatomy.
- If unstable angina is suspected, he should be admitted to hospital.
- An urgent electrocardiogram is mandatory, but even if normal, coronary angiography to visualise coronary anatomy with consideration of revascularisation may be preferable to investigations such as stress testing.
- He should take antiplatelet therapy with modification of risk factors and urgent investigation.

Discussion

What is atherosclerosis?

Atherosclerotic lesions or atheromata are asymmetric focal thickenings on the arterial intima comprising cells (blood-borne inflammatory and immune cells, endothelial cells and smooth muscle cells), connective tissue, lipids and debris.

Is atherosclerosis an inflammatory disease?

Inflammation plays a key role in CAD. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of these lesions and activation of inflammation can elicit acute coronary syndromes. The inflammatory process may lead to elevated blood levels of inflammatory cytokines and acute-phase reactants including C-reactive protein and interleukin-6 (IL-6).

How do atherosclerotic lesions evolve?

Endothelial activation

Chronic minimal injury to the endothelium is physiological. It occurs at bends and bifurcations of vessels and results from turbulent blood flow. It is enhanced by hypertension and induced by hypercholesterolaemia, tobacco toxins, advanced glycation end products in diabetes and possibly infection. But this minimal injury, sometimes referred to as endothelial dysfunction, encourages low-density lipoprotein (LDL), laden with cholesterol, to enter the subendothelial space and bind to subendothelial extracellular matrix. Here, LDL becomes trapped and subject to oxidation or enzyme attack by resident cells, including endothelial and smooth muscle cells and macrophages.

Chemokines and adhesion molecules

Modified LDL particles stimulate monocyte chemotactic protein 1 (MCP-1) synthesis and release from resident cells. MCP-1 is a chemokine that attracts circulating monocytes; these adhere to the endothelial wall facilitated by adhesion molecules such as vascular-cell adhesion molecule 1 (VCAM-1) before entering the subendothelial space.

Macrophages in the developing plaque

Modified LDL also stimulates macrophage colony-stimulating factor production by resident cells, enabling monocytes to differentiate into macrophages. Macrophages take up the modified LDL, apolipoprotein B100 on LDL being recognised by macrophage scavenger receptors, and become foam cells; these are so named because they have a foamy appearance when laden with fat. This process is critical for development of atherosclerosis. Toll-like receptors also bind with pathogen-like material but, in contrast to scavenger receptors, they can initiate cell activation and may be important in plaque inflammation.

T-cell activation and vascular inflammation

Antigens presented by macrophages and antigen-presenting cells trigger the activation of antigen-specific T lymphocytes in the artery, most of which produce T-helper type 1 (Th1) cytokines (e.g. interferon-γ), which activate macrophages and vascular cells, leading to inflammation. Some counter-regulatory Th2 and anti-inflammatory cytokines are also activated (e.g. IL-10, transforming growth factor-β), but atherosclerosis is dominated by a Th1-mediated pro-inflammatory response. The pro-inflammatory versus anti-inflammatory balance dictates progression of atherosclerosis.

Types of atherosclerotic lesion

Early lesions, containing foam cells, are common from the first decade. Foam cells eventually undergo necrosis and discharge their fat, together with necrotic debris, into the extracellular space. The earliest atherosclerotic lesion, the fatty streak, has the beginnings of an extracellular connective tissue matrix streaming through extracellular fat, and represents a dynamic balance between entry and exit of lipoprotein, and between development and breakdown of matrix. Essentially, if more lipoprotein exits the fatty streak than enters (e.g. by risk modification), scarring with minimal risk results; if more lipoprotein enters than exits, vulnerable lesions form. These occur as early as the third decade. Vulnerable atheromatous lesions are soft with a core of foam cells and extracellular lipid and a thin fibrous cap. Macrophages and T cells are abundant, particularly in the 'shoulder region' (between evolving plaque and vessel wall), where atheroma grows. More mature lesions contain increasing amounts of connective tissue, derived from proliferating smooth muscle cells migrating from the media to the intima, forming a firmer fibrous cap.

Treatment implications

Thus the pathophysiology is very complex at a biological level but relatively simple at a practical level. The overall progression of coronary artery lesions is fatty streaks leading to smooth muscle proliferation and plaques which have the potential to rupture, provoking platelet aggregation and acute coronary syndromes. This has not changed over the years, but improved understanding has improved treatment. In the 1980s angina was treated symptomatically, myocardial infarction was managed at home, possibly after streptokinase. In the 1990s angina was still very much a primary care disease, myocardial infarction was thrombolysed but there was still relatively little secondary prevention. In the 2000s angina was increasingly referred to hospital with a massive increase in angiography and percutaneous intervention, thrombolysis in myocardial infarction was increasingly replaced by primary percutaneous coronary intervention and acute coronary syndromes overall were recognised as very dangerous with increasing infrastructure for their inpatient management and rapid access chest pain services.

How do atherosclerotic plaques rupture?

Angiographically, small plaques are often the most vulnerable to disruption, provoking thrombus formation with stenosis or total vessel occlusion. Plaque disruption may be passive, in which the thin fibrous cap mechanically erodes, fissures or ruptures, frequently at the plaque's shoulder, or active, in which several cells, including macrophages and T cells, destabilise lesions by producing proteolytic enzymes such as matrix metalloproteinases and cysteine proteases, inflammatory cytokines, coagulation factors, radicals and vasoactive molecules.

How do acute coronary syndromes arise?

Tissue factor is exposed after plaque rupture and initiates the extrinsic coagulation pathway, and thrombus forms on the disrupted plaque to occlude the vessel. Platelet-induced vasoconstriction can exacerbate vessel occlusion. Angina results when myocardial oxygen demand outweighs the supply that stenosed vessels can provide. Angina may occur when a plaque produces a > 50% diameter stenosis (or > 75% reduction in cross-sectional area). In acute coronary syndromes there is invariably some degree of plaque disruption with superimposed thrombosis and vasoconstriction. The type of acute coronary syndrome depends upon the lesion, the degree of natural reversibility from spontaneous thrombolysis and the degree of safety netting from collateral vessels. Myocardial infarction in patients with no antecedent ischaemia is often more catastrophic. Clinical patterns of coronary artery disease depending upon pathophysiology are listed in Table 2.16.

How is stable angina diagnosed?

Stable angina is characterised by a pattern of symptoms occurring predictably on exertion. Unstable angina refers to symptoms of recent onset, symptoms increasing in frequency, severity or duration, or symptoms occurring at rest. It suggests plaque instability, and is a medical emergency. All patients with newly diagnosed cardiac pain should presumptively be considered to have unstable disease. National Institute for Health and Clinical Excellence guidelines advocate a system for establishing the likelihood of stable angina as the cause of non-acute chest pain that considers clinical assessment and typicality of angina pain, diagnostic testing and making the diagnosis, as follows.

Table 2.16 Types of coronary artery disease depending upon pathophysiology

Pathophysiology	Clinical pattern of coronary artery disease
Platelet aggregation (*de novo*)	Asymptomatic, ACS or MI
Fatty streaks	Asymptomatic, ACS or MI
Minor plaque / thin cap (not occlusive)	Asymptomatic, ACS or MI (most cases of ACS or MI caused by this as unstable)
Occlusive plaque / thick cap	Angina (most cases of angina as lesions more stable)
Total occlusion	Cold start angina, especially susceptible if also anaemic
Coronary artery spasm / intrinsic (e.g. Takotsubo cardiomyopathy)	Atypical angina, ACS or MI
Coronary artery spasm / extrinsic (e.g. cocaine)	ACS or MI
Other possible factors, e.g. catecholamines, infection, free radicals	Angina, ACS or MI

ACS, acute coronary syndrome (includes unstable angina and different types of MI); MI, myocardial infarction.

Clinical assessment and typicality of angina pain

1. Constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arm
2. Precipitated by physical exertion
3. Relieved by rest or glyceryl trinitrate within about 5 minutes

Three features are defined as typical angina. Two of the three features above are defined as atypical angina. One or none of the features are defined as non-anginal chest pain. Clinical assessment and typicality of angina pain may be used to estimate the likelihood of CAD (Table 2.17).

Diagnostic testing

- If people have features of typical angina and their estimated likelihood of CAD is greater than 90%, further diagnostic investigation is unnecessary and it should be managed as angina.
- Unless clinical suspicion is raised based on other aspects of the history and risk factors, a diagnosis of stable angina is excluded if pain is non-anginal. If

Table 2.17 Percentage of people estimated to have coronary artery disease according to typicality of symptoms, age, sex and risk factors

	Non-anginal chest pain				**Atypical angina**				**Typical angina**			
	Men		**Women**		**Men**		**Women**		**Men**		**Women**	
Age (years)	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

For men older than 70 with atypical or typical symptoms, assume an estimate > 90%.
For women older than 70, assume an estimate of 61–90% *except* women at high risk *and* with typical symptoms where a risk of > 90% should be assumed.
Values are per cent of people at each mid-decade age with significant coronary artery disease (CAD).
Hi, high risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47 mmol / l).
Lo, low risk = none of these three.
If there are resting electrocardiogram ST–T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

the estimated likelihood of CAD is less than 10%, causes of chest pain other than angina caused by CAD should be considered.

- In people without confirmed CAD in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, further diagnostic testing is indicated as follows:
  - If the estimated likelihood of CAD is 61–90%, *invasive coronary angiography* is the first-line diagnostic investigation if appropriate.
  - If the estimated likelihood of CAD is 30–60%, *functional imaging* is the first-line diagnostic investigation. Non-invasive functional testing may be myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or stress echocardiography or first-pass contrast-enhanced magnetic resonance (MR) perfusion or MR imaging for stress-induced wall motion abnormalities (MR is evolving for identifying coronary artery disease, myocardial infarction, downregulating hibernating myocardium in response to stress and heart failure). Stress agents are adenosine, dipyridamole or dobutamine for MPS with SPECT, adenosine or dipyridamole for first-pass contrast-enhanced MR perfusion, and exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities.
  - If the estimated likelihood of CAD is 10–29%, *CT calcium scoring* is the first-line diagnostic investigation (but many cardiologists feel that CT has greater applicability).
- Exercise electrocardiogram testing should not be used to diagnose or exclude stable angina for people without known CAD, and MR coronary angiography should not be used either.
- For people with confirmed CAD (for example, previous myocardial infarction, revascularisation, previous angiography) in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, functional imaging or exercise electrocardiogram testing may be considered.

Box 2.21 **Definition of significant coronary artery disease (CAD)**

Significant CAD found during invasive coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery.

Factors intensifying ischaemia

Such factors allow less severe lesions (for example ≥ 50%) to produce angina:

- Reduced oxygen delivery: anaemia, coronary spasm
- Increased oxygen demand: tachycardia, left ventricular hypertrophy
- Large mass of ischaemic myocardium: proximally located lesions
- Longer lesion length

Factors reducing ischaemia

Such factors may render severe lesions (≥ 70%) asymptomatic:

- Well-developed collateral supply
- Small mass of ischaemic myocardium
- Distally located lesions
- Old infarction in the territory of coronary supply

Making the diagnosis

Stable angina is diagnosed when significant CAD is found during CT coronary angiography and/or reversible myocardial ischaemia is found during non-invasive functional imaging. Significant CAD on invasive coronary angiography is defined in Box 2.21. Other causes of chest pain should be considered if significant CAD is not found during invasive coronary angiography or CT coronary angiography and/or reversible myocardial ischaemia is not found during non-invasive functional imaging or the calcium score is zero.

Some important rules of judgement

Some important rules of judgement, not in guidelines, are outlined in Box 2.22.

Which angiographic lesions tend to pose a higher risk?

Certain features suggest higher risk. These include diffuse rather than discrete lesions, eccentric rather than concentric lesions, proximal tortuosity rather than a readily accessible lesion, moderate or heavy calcification and involvement of major side branches.

Box 2.22 **Important rules of judgement in diagnosing stable angina**

Rather than emphasis on the nature of symptoms, key discriminating factors that favour angina are:

- Duration of recovery (< 30 minutes)
- Exacerbating factors (cold, meals, exercise)
- Reproducibility (unlike acute coronary syndromes where symptoms are abrupt, not reproducible but often variable and certainly not classical, reflecting dynamic pathology)
- The likelihood of the patient having the underlying pathology of coronary artery disease (most importantly, perhaps)

'Probabilities' of angina are as follows:

- Low probability: atypical symptoms / no risk factors; typical symptoms / no risk factors
- Moderate probability: atypical symptoms / high-risk factors; typical symptoms / moderate risk factors in female
- High probability: typical symptoms / moderate risk factors in male; atypical symptoms but from Indian subcontinent
- 'Dead cert': typical symptoms / high-risk factors; peripheral vascular disease!

How is stable angina managed?

Medical management as the initial, sometimes only, treatment strategy has become more evidence based in recent years. Cardiologists and cardiac surgeons also need to respond to the changing evidence base underpinning choice of revascularisation strategy (particularly for patients with left main and three-vessel coronary artery disease) and recognise that evidence for revascularisation on prognostic grounds is based on old trials conducted before the introduction of secondary prevention treatments that also improve prognosis. Management principles are outlined in Box 2.23.

How important is reducing heart rate in coronary heart disease and what agents may be used to effect this?

The association of heart rate with total and / or cardiovascular mortality is significant because a faster rate increases arterial wall stress and the likelihood of development of atherosclerosis and plaque rupture.

- Beta blockers are first-line agents.
- Rate-limiting calcium channel blockers have symptomatic but no clear prognostic benefits.
- I_f inhibitors (ivabridine) block the sinus node directly via an inward depolarising current to produce pure reduction in heart rate. There are no beta-blocking side effects but visual disturbance may occur because I_f receptors are present in the retina.

Box 2.23 **Managing stable angina**

General measures

- The long-term management should be explained to patients, who should be aware of factors that can provoke angina. A useful source of information is the British Heart Foundation. Lifestyle advice – e.g. weight control, diet, stopping smoking, and exercise – is important. There is no evidence for vitamin or fish oil supplements, although n-3 fatty acids and vitamins E, C and B remain potentially protective.

Preventing and treating episodes of angina

- A short-acting nitrate is helpful for preventing and treating episodes of angina, and immediately before planned exertion. Side effects include flushing, headache and pre-syncope. The dose may be repeated after 5 minutes if pain has not gone, and an emergency ambulance called if the pain has not gone 5 minutes after the second dose.

Drug treatment

- Optimal initial drug treatment consists of one or two anti-angina drugs as necessary to treat symptoms plus drugs for secondary prevention of cardiovascular disease. The purpose of treatment, importance of taking drugs regularly, and how side effects might affect daily activities should be explained. Drugs should be titrated against symptoms to maximum tolerable dosage, and responses reviewed.

Anti-angina drugs

- A *beta blocker* or a *calcium channel blocker* is first line. If symptoms are not satisfactorily controlled, switching to the other or using a combination of the two is recommended.
- For people taking either a beta blocker or calcium channel blocker alone whose symptoms are not controlled and the other option is contraindicated or not tolerated, the following may be considered as an addition: a *long-acting nitrate*; *ivabradine*, a selective inhibitor of pacemaker activity in the sinus node; *nicorandil*, a vasodilator; *ranolazine*, which acts on intracellular sodium currents to reduce myocardial ischaemia.
- When combining a calcium channel blocker with either a beta blocker or ivabradine, a dihydropyridine calcium channel blocker – e.g. slow release nifedipine, amlodipine or felodipine – should be used. If beta blockers or calcium channel blockers cannot be tolerated or are contraindicated, monotherapy with a long-acting nitrate or ivabradine, nicorandil or ranolazine should be considered.

Box 2.23 **Managing stable angina—cont'd**

- A third drug may be added when symptoms are not controlled satisfactorily with two anti-angina drugs and revascularisation is awaited or not considered appropriate or acceptable.

Drugs for secondary prevention of cardiovascular disease

- Aspirin 75 mg daily for people with stable angina should be considered, taking into account the risk of bleeding and comorbidities.
- Statin therapy and treatment for high blood pressure in line with guidelines on lipid modification and hypertension should be offered.
- Angiotensin-converting enzyme inhibitors should be considered for people with stable angina and diabetes and continued in patients taking these for other indications.

When symptoms are not controlled satisfactorily on optimal medical treatment

- Revascularisation should be considered, with coronary angiography to guide treatment strategy. Additional non-invasive (e.g. dobutamine stress echocardiography, myocardial perfusion imaging) or invasive functional testing (measurement of coronary artery fractional flow reserve) may be required to evaluate angiographic findings and guide treatment decisions. The options are percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. The risks and benefits of PCI and CABG surgery for people with anatomically less complex disease should be explained, and where the person does not express a preference, PCI is offered in preference to CABG surgery as the more cost-effective strategy. There is potential survival advantage associated with CABG surgery compared with PCI for people with multivessel disease who have diabetes, are over 65 years, or have anatomically complex three-vessel disease, with or without involvement of the left main stem.

When symptoms are controlled satisfactorily on optimal medical treatment

The following should be considered and discussed:

- Prognosis without further investigation
- The low likelihood of their having left main stem disease or proximal three-vessel disease
- The availability of CABG surgery to improve prognosis in the small subgroup of people with left main stem or proximal three-vessel disease
- The process and risks of investigation and the benefits and risks of CABG surgery, including the potential survival gain – e.g. in people with left main stem disease, such surgery may extend survival by a mean of 19 months over 10 years.

After discussion, a functional test or non-invasive anatomical test (computed tomography angiography) may be considered to identify people who might gain survival benefit from surgery. If functional testing indicates extensive ischaemia or non-invasive anatomical testing demonstrates the likelihood of left main stem or proximal three-vessel disease, and if revascularisation is acceptable and appropriate, coronary angiography is considered, and if it indicates left main stem disease or proximal three-vessel disease, CABG surgery.

General principles of revascularisation

A multidisciplinary team including interventional cardiologists and cardiac surgeons should discuss the risks and benefits of continuing drug treatment or revascularisation strategy (CABG surgery or PCI) for people with stable angina. Treatment strategy should be considered for, but not be limited to, people with left main stem or anatomically complex three-vessel disease, and people in whom doubt exists about the best method of revascularisation because of the complexity of the coronary anatomy, the extent of stenting required, or other relevant clinical factors and comorbidities. The main purpose of revascularisation is to improve the symptoms of stable angina, but repeat revascularisation may be necessary after either procedure, although the rate is lower after CABG surgery. Stroke is an uncommon complication of each of the two procedures (incidence similar). There is a potential survival advantage with CABG surgery for some people with multivessel disease.

Stable angina that has not responded to treatment

For people whose stable angina has not responded to drug treatment and/or revascularisation, re-evaluation should include exploring alternative diagnoses and the person's perceptions of the condition and its pain. There is no evidence for transcutaneous electrical nerve stimulation, enhanced external counterpulsation, or acupuncture to manage stable angina.

CASE 2.9 ACUTE CORONARY SYNDROME

Candidate instructions

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr William Harwood, aged 62 years

Thank you for admitting Mr Harwood, who has had 2 hours of chest pain this morning. This came on while gardening and did not settle with his usual glyceryl trinitrate spray but has now settled with morphine 5 mg at the surgery. He had a coronary stent inserted in his right coronary artery 6 weeks ago and I am clearly concerned about unstable coronary disease. I have given him aspirin 300 mg. I have taken an ECG, which shows T-wave inversion in the inferior leads, but I think this may be old.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient instructions

Mr William Harwood is a 62-year-old man who has just arrived at the hospital after experiencing angina-like chest pain for 2 hours this morning. This came on while gardening and did not settle with three sprays of glyceryl trinitrate (GTN) but it eventually settled with morphine at the GP's surgery, to where he managed to drive. He did not want to call an ambulance because he did not want to come to hospital. His wife has severe osteoporosis and has been troubled recently with severe back pain because of a vertebral compression fracture rendering her immobile; she is awaiting a review by the orthopaedic specialist. Mr Harwood is her main carer. He has had a previous heart attack and had a coronary stent inserted in his right coronary artery 6 weeks ago and knows in himself that there is very likely a problem with the stent because if anything his angina has been worse since it was inserted. He has tried to ignore it, hoping that his medications will work. He was told by the hospital doctor last time that the medications he takes should 'protect the heart' and he had hoped that this would be the case even if he were experiencing pain. He does not smoke. His medications are aspirin 75 mg, clopidogrel 75 mg, simvastatin 40 mg, atenolol 50 mg, ramipril 10 mg, all daily, and GTN.

How to approach the case

Data gathering in the interview and interpretation and use of data gathered

Presenting problem(s) and symptom exploration

The definition of an acute coronary syndrome (ACS) is given in Box 2.24.

Box 2.24 Acute coronary syndrome – definitions

The term acute coronary syndrome (ACS) refers to a spectrum of presentations caused by myocardial ischaemia that includes unstable angina, non-ST elevation myocardial infarction (NSTEMI) – collectively NSTE-ACS – and ST elevation myocardial infarction (STEMI). The embracing term reflects the common pathophysiology of plaque disruption, intravascular thrombosis and impaired myocardial blood supply. However, STEMI is the result of complete epicardial occlusion following plaque disruption and leads to propagation of thrombus and epicardial vasoconstriction / spasm, but NSTEMI is incomplete and transient epicardial occlusion with platelet-rich thrombus and phasic distal embolisation occurs. Troponin assays have confirmed that many patients with what might have formerly been attributed to unstable angina do in fact sustain myocardial damage and have had a NSTEMI.

Unlike stable angina (Case 2.8), an ACS is associated with relatively short and sudden development of symptoms. These are not reproducible, often variable and certainly not classical (e.g. exercise may provide relief of symptoms by changing coronary artery spasm), reflecting dynamic pathology. This said, an ACS is unlikely if symptoms do not seem familiar to patients with known coronary disease. Subtle symptoms may herald the onset of chest pain. 'Indigestion'-like symptoms with minor left hand numbness may be more common with an inferior territory ACS (at least 25% of patients insist their ACS is indigestion), and symptoms may be too subtle for the patient to call an ambulance. Risk factors are important, but occasionally people with no risks suffer an ACS. There is no algorithm for such a complex syndrome, but experienced senior review of history and risk factors is essential, and where history is persuasive at any age, or where risk factors are present, suspicion should be high.

■ **Ask about the chest pain.** Ask about:

- The site, character and radiation of chest pain
- The onset, evolution and duration of symptoms
- Any precipitating, exacerbating or relieving factors
- How it settled (did the GTN have any impact – though GTN responsiveness is not very helpful as chest pain waxes and wanes anyway, or was it only with the oxygen and morphine, and has it now settled completely?)
- Its intensity (was this as bad as his original heart attack?).

■ **Ask about associated symptoms.** Ask about:

- Dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and ankle swelling
- Syncope or presyncopal symptoms (aortic stenosis).

■ **Ask about progress.** Ask about details of any action / treatment en route to hospital by the ambulance crew and ask what he has been told so far about what is suspected to be wrong.

■ **Consider the differential diagnosis of acute chest pain.** The differential diagnosis includes all causes of chest pain (Case 2.8), not least dyspepsia from aspirin and clopidogrel. If aortic dissection is considered in the differential diagnosis, immediate imaging with computed tomography (CT) / magnetic resonance imaging is needed, a chest radiograph being unhelpful in this context.

Patient perspective

Reassure him that he did the right thing in agreeing to come to hospital, and that, while the medications are somewhat protective, if he is having pain it may well mean that there is a problem with one of the arteries that needs urgent attention.

Past medical history

His cardiovascular disease (CVD) risk factors will need to be reviewed to ensure that optimal medical therapy is on board but immediately he needs exclusion of and presumptive treatment for an ACS.

Drug and allergy history

His medications are all very reasonable.

Family history

There may or may not be a family history of coronary disease, but the relevance of that is historical; he has coronary disease and is by definition at high risk.

Social history

Explore who might be in a position to care for his wife if he is in hospital for a few days.

SUMMARY BOX – ASSESSMENT AND PLAN

- He has had an acute coronary syndrome until proven otherwise.
- He should have routine blood tests, serial electrocardiograms and a troponin level taken 6–12 hours after the time of maximal pain.
- He should be commenced on low-molecular-weight heparin.
- Early liaison with his cardiologist is needed for consideration of repeat coronary angiography.

Discussion

What are the causes of a raised cardiac troponin level and how do you interpret results?

Cardiac causes include myocardial infarction, arrhythmias, coronary vasospasm, cardiomyopathy, myocarditis, amyloidosis, contusion, coronary intervention, surgery and cardioversion/implantable cardioverter defibrillator shocks. Non-cardiac causes include critical illness, chemotherapy, primary pulmonary hypertension, pulmonary embolism, hypertensive crises, renal failure, subarachnoid haemorrhage, sepsis, stroke and ultra-endurance exercise.

Troponin predictive accuracy is very dependent on the pre-test probability of ACS. If troponin is positive in a typical patient ACS treatment should be started. If positive in an atypical patient an open mind should be kept. A slightly elevated troponin at 12 hours unchanged from an earlier one is probably not due to an ACS unless clinical features are compelling. Troponins should not undermine the value of serial electrocardiograms.

Are other markers of myocardial damage on the horizon?

Troponin testing has improved identification of high-risk patients but there is room for refinement of markers. The vascular inflammation that occurs at the time of an ACS may yield new markers and the CD40 ligand is a marker of future events in ACSs.

Which electrocardiogram leads are affected in each type of myocardial infarction?

Most ACSs have no acute electrocardiogram changes. II, III, aVF (inferior leads) indicate right coronary artery (RCA) territory disease. I, aVL, V5, V6 (lateral leads) indicate left circumflex artery territory disease. V1–V5 (anterior leads) indicate left anterior descending (LAD) territory disease. Posterior ST elevation myocardial infarctions (STEMIs) can produce profound reciprocal ST depression in V1–V4 with prominent R waves and/or ST elevation in leads V7–V9 placed horizontally under the left scapula at the level of V4–V6.

Box 2.25 **Thrombolysis In Myocardial Infarction (TIMI) score**

1. Age ≥ 65
2. Three or more risk factors for coronary disease
3. More than 50% coronary stenosis on angiography
4. ST segment change ≥ 0.5 mm
5. Two or more anginal episodes in 24 hours before presentation
6. Elevated serum cardiac markers
7. Use of aspirin in 7 days before presentation

One point is scored for each variable. The score is interpreted as:

- 0–2: low risk
- 3–4: intermediate risk
- 5–7: high risk.

The situation can clearly change in subsequent days; furthermore, some think that troponin concentrations should qualify for more than one point.

What systems are there for stratifying ACS risk?

The Thrombolysis In Myocardial Infarction (TIMI) score is an objective means of risk stratification intended for acute 'through the door' decision making based on seven variables (Box 2.25).

The Global Registry of Acute Coronary Syndromes (GRACE) system uses the following predictors of death – age, Killip class (heart failure), heart rate, blood pressure, ST deviation, cardiac arrest, raised creatinine or raised cardiac enzymes. It is used at initial assessment to predict 6-month mortality and risk of future adverse cardiovascular events and so guide management (Table 2.18).

Summarise antiplatelet therapy in non-ST elevation acute coronary syndrome (NSTE-ACS)

Platelets were once considered little more than inert smudges on a blood film with a role in clotting. Over 80 surface receptors have now been identified, many involved in platelet activation. Platelet function may be assessed by various laboratory techniques involving addition of activation agonists to a blood sample and assessing platelet 'clump-ability'. Equally, by adding platelet antagonistic drugs to blood samples and assessing the variable responses, it is possible to determine individual likelihoods of responding to particular drugs; for example, the level of breakdown products of thromboxane A_2 in urine can help determine whether or not aspirin is effective, lower levels indicating greater effect. Potential sites determining variability of response to antiplatelet drugs include

Table 2.18 Global Registry of Acute Coronary Syndromes (GRACE) risk stratification

Predicted 6-month mortality (%)	Risk of future adverse cardiovascular events
≤ 1.5	Lowest
> 1.5–3.0	Low
> 3.0–6.0	Intermediate
> 6.0–9.0	High
> 9.0	Highest

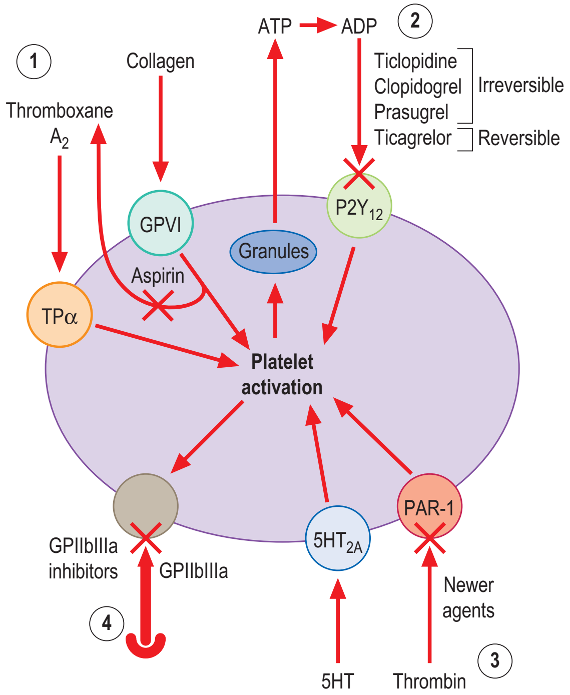


Figure 2.5 Antiplatelet agents. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GP, glycoprotein; 5-HT, 5-hydroxytryptamine; PAR-1, protease activated receptor-1; P2Y, a type of purinergic receptor; TP, thromboxane platelet receptor.

gut absorption, liver metabolism, and platelet receptor genetic polymorphisms. Platelet adhesion, activation and aggregation occur at sites of endovascular damage (Case 2.34). Platelet activation results from the binding of various agonists (e.g. thomboxane A_2, collagen, adenosine diphosphate (ADP), thrombin, arachidonic acid) to specific receptors leading to intracellular changes. During activation the platelet GPIIbIIIa receptor undergoes a conformational change, allowing it to bind to the dimeric fibrinogen molecule, and irreversible platelet aggregation occurs. This platelet plug is the troublemaker in ACSs and other thrombotic events. Drugs interfere with platelet function usually by inhibiting platelet activation, although some inhibit platelet aggregation. These are illustrated in Figure 2.5 and may be broadly classified as follows.

1. Aspirin

Aspirin (acetylsalicylic acid) inhibits isoenzyme cyclooxygenase 1 (COX-1) leading to suppression of thromboxane A_2 production. This action is irreversible, but platelet lifespan is only up to 10 days and new recruits continuously exit their bone marrow barracks, and so the need for daily dosing. But, as seen in Figure 2.5, aspirin only partially interferes with platelet activation; an army of alternative receptors and molecules are waiting to activate platelets.

2. ADP pathway antagonists – $P2Y_{12}$ receptor inhibitors

ADP is a powerful amplifying trigger of platelet activation. Many pathways that activate platelets result in platelet granule release and production of ADP, which via the platelet adenosine nucleotide receptor $P2Y_{12}$ amplifies the activation. Thienopyridine drugs such as ticlodipine (not used now on account of side effects), clopidogrel and prasugel are selective and irreversible inhibitors of this receptor and so inhibit binding of ADP to platelet receptors and so inhibit ADP-induced adenylcyclase activity. Reversible inhibitors of this receptor include AZD6140/cangrelor/ticagrelor. Inhibition of ADP receptor binding also deactivates the platelet GPIIbIIIa complex, thereby inhibiting platelet aggregation.

Since clopidogrel and aspirin act on different platelet receptors, dual use confers additive effects. The CURE study was the first to demonstrate this and showed a 20% relative risk reduction in NSTE-ACS with the combination of clopidogrel (300 mg loading dose, followed by 75 mg daily) and aspirin compared with aspirin alone, whether or not patients proceeded to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The CHARISMA study did not reproduce these results, but was flawed by the inclusion of patients following an ACS (who did benefit from clopidogrel) and those at high risk taking clopidogrel for primary prophylaxis (who did not benefit) – in other words, those who had a clot benefited. The CREDO study showed that clopidogrel did not start to produce benefits until after around 15 hours. The CLASSICS trial established the role of clopidogrel following PCI. The PCI-CURE study, a subgroup analysis of the CURE trial, further established the role of clopidogrel after coronary stenting.

Prasugrel produces more rapid and consistent platelet inhibition than clopidogrel and does not appear to be affected significantly by proton pump inhibitors, or loss-of-function variants of the *CYP2C19* gene and evidence for benefit comes from trials including the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON-TIMI) trial. The rate of adverse effects, such as thrombocytopenia or neutropenia, was similar with prasugrel and clopidogrel.

Ticagrelor evidence for benefit comes from trials including the PLATelet inhibition and patient Outcomes (PLATO) trial in moderate- to high-risk NSTE-ACS (planned for

Box 2.26 **Use of antiplatelet therapy in non-ST elevation acute coronary syndrome**

Aspirin

- Aspirin should be given to all patients without contraindications (bleeding risk or hypersensitivity) at an initial loading dose of 300 mg, and at a maintenance dose of 75–100 mg daily long term regardless of treatment strategy. For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered.
- Non-steroidal anti-inflammatory drugs may reversibly block cyclo-oxygenase 1 (COX-1) and prevent irreversible inhibition by aspirin as well as causing potentially prothrombotic effects via COX-2 inhibition and should be avoided.

P2Y$_{12}$ inhibitors

- A P2Y$_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. A proton pump inhibitor (preferably not omeprazole) in combination with dual (oral) antiplatelet treatment (DAPT) is recommended where there is a history of gastrointestinal haemorrhage or peptic ulcer, and is appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).
- Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponin), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).
- Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for P2Y$_{12}$-inhibitor-naive patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to percutaneous coronary intervention (PCI) unless there is a high risk of life-threatening bleeding or other contraindications.
- Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel who have a predicted 6-month mortality of > 1.5% or who may undergo PCI within 24 hours of admission provided there are no contraindications (National Institute for Health and Clinical Excellence guidelines predated European Society of Cardiology guidelines and recommend clopidogrel without consideration of other P2Y$_{12}$ inhibitors). A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy – higher doses produce faster and greater platelet inhibition. A higher maintenance dose of clopidogrel of 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding. Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.
- Interruption of DAPT soon after stent implantation increases the risk of subacute stent thrombosis, which carries a particularly adverse prognosis, with mortality varying from 15% to 45% at 1 month. In patients pre-treated with P2Y$_{12}$ inhibitors who need to undergo major surgery (including coronary artery bypass grafting (CABG)), postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, should be considered unless the patient is at high risk of ischaemic events. The optimal timing of restarting medication following CABG surgery remains uncertain.

GPIIbIIIa inhibitors

- Intravenous eptifibatide or tirofiban may be used as part of early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality > 3.0%) and who are to undergo angiography within 96 hours of hospital admission.
- Abciximab is an adjunct to PCI for patients at intermediate or higher risk not already receiving a GPIIbIIIa inhibitor.

either conservative or invasive management) or STEMI planned for primary PCI randomised to either clopidogrel or ticagrelor. Co-administered with aspirin, the PLATO trial showed that, for every 72 patients with an ACS treated for 12 months with ticagrelor instead of clopidogrel, one extra life was saved.

3. Emerging platelet receptor antagonists

There is a need to find alternative ways around the problems of partial inhibition of platelet activation and platelet receptor genetic polymorphism-induced resistance. As well as evaluating different doses of the above drugs, researchers are looking at alternative platelet receptors such as protease-activated receptor-1 (PAR-1).

4. GPIIbIIIa inhibitors

GPIIbIIIa inhibitors block the platelet receptor for fibrinogen and hence prevent sandwiching of fibrinogen between platelets and the final common pathway of aggregation. These were demonstrated to be effective in ACS, especially in those people with troponin positivity or undergoing PCI, in trials such as CAPTURE, PURSUIT, PRISM, PRISM-PLUS, PARAGON-B, ACUITY Timing and EARLY-ACS. Oral GPIIbIIIa inhibitors have not been shown to be very effective. The drugs in current use are abciximab, eptifibatide and tirofiban.

Recommended usage of antiplatelet therapy in NSTE-ACS is given in Box 2.26.

Summarise antithrombin therapy in NSTE-ACS

Antithrombin anticoagulant drug mechanisms are discussed in detail in Case 2.36 (Deep vein thrombosis). Recommended usage of antithrombin therapy in NSTE-ACS is given in Box 2.27.

Summarise the use of anti-ischaemic drugs in NSTE-ACS

Anti-ischaemic drugs either decrease myocardial oxygen demand (by decreasing heart rate, lowering blood pressure, reducing preload, or reducing myocardial contractility) or increase myocardial oxygen supply (by inducing coronary vasodilatation).

Box 2.27 Use of antithrombin therapy in non-ST elevation acute coronary syndrome

The heparins – low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) – inhibit thrombin (IIa) and Xa via antithrombin

LMWH compared with UFH is as effective, more practical, does not require monitoring and side effects, such as heparin-induced thrombocytopenia (HIT), are fewer. A mild self-limiting form of HIT is common and a more dangerous immune-mediated form occurs infrequently in patients exposed to treatment for longer than 5 days.

Indirect thrombin inhibitors

However, fondaparinux, a direct thrombin inhibitor, has been shown to be superior to LMWH in acute coronary syndrome management. Fondaparinux is used for patients who do not have a high bleeding risk unless angiography is planned within 24 hours of admission. Systemic UFH (50–100 units/kg) is used as an alternative to fondaparinux if angiography is likely within 24 hours of admission, and in those with significant renal impairment, and in patients on fondaparinux undergoing percutaneous coronary intervention (PCI).

Direct thrombin inhibitors

Bivalirudin is an alternative to the combination of a heparin plus a GPIIbIIIa inhibitor and may be considered for patients at intermediate or higher risk (predicted 6-month mortality > 3%) not already receiving a GPIIbIIIa inhibitor or fondaparinux who are scheduled for angiography (with follow-on PCI if indicated) within 24 hours of admission or undergoing PCI.

Beta blockers

These competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and contractility. The evidence for benefit is extrapolated from early studies in STEMI and stable angina patients, more recent double-blind randomised trials compared with placebo in unstable angina, and meta-analysis studies suggesting a 13% relative risk reduction of progression to STEMI. No significant effect on mortality in NSTE-ACS has been demonstrated. Reservations about giving beta blockers came from the Chinese Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study in mostly STEMI patients, which resulted in a significantly higher rate of cardiogenic shock with metoprolol, but overall meta-analysis data favour beta blockers.

Nitrates

The use of nitrates in unstable angina is largely based on pathophysiological considerations and clinical experience. The major therapeutic benefit is probably related to the venodilator effects that lead to a decrease in myocardial preload and left ventricular end-diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal as well as atherosclerotic coronary arteries and increase coronary collateral flow.

Calcium channel blockers

These are vasodilators. In addition, some have direct effects on atrioventricular conduction and heart rate. There are three subclasses of calcium blockers: dihydropyridines (such as nifedipine), benzothiazepines (such as diltiazem), and phenylethylamines (such as verapamil). Atrioventricular block may be induced by non-dihydropyridines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation, whereas diltiazem has the least vasodilatory effect. All subclasses cause similar coronary vasodilatation. Evidence of the effect on prognosis in NSTE-ACS patients is limited. Most of the data with dihydropyridines show no significant benefit in either myocardial infarction or post-myocardial infarction secondary prevention but a trend for harm, whilst studies with verapamil and diltiazam suggest reductions in sudden death, re-infarction and total mortality, with the largest benefit in patients with preserved left ventricular function.

Other anti-anginal drugs

Nicorandil, a potassium channel opener, reduced the rate of the primary composite endpoint in patients with stable angina, but was never tested in ACS patients. Ivabradine selectively inhibits the primary pacemaker in the sinus node and may be used in selected patients with beta-blocker contraindications. Ranolazine exerts anti-anginal effects by inhibiting the late sodium current and was not effective in reducing major cardiovascular events in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-elevation Acute Coronary Syndromes (MERLIN) study.

Recommended use of anti-ischaemic drugs in NSTE-ACS is given in Box 2.28.

Summarise revascularisation strategies in NSTE-ACS

These may relieve symptoms and improve prognosis. Risk stratification should be performed as early as possible.

Invasive versus conservative approach

Those who may benefit from an invasive strategy are outlined in Box 2.29.

PCI versus CABG

There are no specific trials comparing PCI with CABG in patients with NSTE-ACS. In patients stabilised after an episode of ACS, the choice of revascularisation modality can be made as in stable angina (Case 2.8). The revascularisation strategy (culprit lesion PCI/multivessel PCI/CABG) should be based on clinical status as well as disease severity, i.e. distribution and angiographic lesion characteristics. PCI of non-significant lesions is not recommended.

Box 2.28 **Use of anti-ischaemic drugs in non-ST elevation acute coronary syndrome**

- Patients on chronic beta-blocker therapy admitted with acute coronary syndrome should be continued on beta-blocker therapy if not in class ≥ III heart failure. Oral beta-blocker treatment is indicated in all patients with left ventricular dysfunction without contraindications. Intravenous beta-blocker treatment at the time of admission should be considered for patients in a stable haemodynamic condition (class < III) with hypertension and/or tachycardia.
- Calcium channel blockers are recommended for symptom relief in patients already receiving nitrates and beta blockers (dihydropyridine type), and in patients with contraindications to beta blockade (non-dihydropyridine type). Calcium channel blockers are recommended in vasospastic angina. Nifedipine or other dihydropyridines are not recommended unless combined with beta blockers.
- Oral or intravenous nitrate treatment is indicated to relieve angina; intravenous nitrate treatment is recommended in recurrent angina and/or signs of heart failure.

Box 2.29 **Invasive management of non-ST elevation acute coronary syndrome**

National Institute for Health and Clinical Excellence guidelines

Recommendations are:

- Angiography (with follow-on percutaneous coronary intervention (PCI) if indicated) as soon as possible for patients who are clinically unstable or at high ischaemic risk
- Angiography within 96 hours of admission for those at intermediate or higher risk when initially assessed (predicted 6-month mortality > 3.0%) if there are no contraindications (such as active bleeding or comorbidity)
- Conservative management without early coronary angiography for those at low risk when initially assessed (predicted 6-month mortality ≤ 3.0%). Angiography (with follow-on PCI if indicated) is indicated if ischaemia is subsequently experienced or demonstrated by ischaemia testing.

European Society of Cardiology guidelines

Primary criteria for invasive management are:

- Relevant rise or fall in troponin
- Dynamic ST- or T-wave changes (symptomatic or silent).

Secondary criteria for invasive management are:

- Diabetes mellitus
- Renal insufficiency (estimated glomerular filtration rate < 60 ml/min/1.73 m^2)
- Reduced left ventricle function (ejection fraction < 40%)
- Early post-infarction angina
- Recent PCI
- Prior coronary artery bypass grafting
- Intermediate to high Global Registry of Acute Coronary Syndromes (GRACE) risk score.

What do you understand by the term drug-eluting stent (DES)?

PCI DESs reduce the rate of in-stent stenosis and the overall need for further revascularisation. However, they do this at the price of an increased risk of stent thrombosis, not seen in bare metal stents. The risk of DES thrombosis is much increased by the premature cessation of dual antiplatelet therapy (DAPT); DAPT is currently recommended for 12 months after DES implantation, and does not seem to be associated with excessive bleeding, although thrombotic risk appears to continue after 12 months. Stent technology is ever changing.

Is bleeding risk from antithrombotic treatment a concern?

As a broad generalisation, patients at highest ischaemic risk are also those who are at higher risk of bleeding complications associated with the use of multiple antiplatelet and antithrombin agents. The addition of warfarin for those who need it poses further risk, with little evidence for guidance, although expert opinion recommends reducing the dose of aspirin to 75 mg daily, minimising the duration of DAPT and a lower international normalised ratio target; temporary discontinuation of warfarin or use of one antiplatelet agent is considered only if the risk of bleeding is deemed to exceed the benefits of treatment. Gastrointestinal prophylactic treatment should be initiated.

What special patient group or comorbidity considerations are there in ACS?

These include:

Older people

The clinical presentation of NSTE-ACS in older people is often atypical and they are more likely to have mild symptoms. This is a more heterogeneous population in terms of disease, comorbidity and functional status. Technical issues with PCI include the fact that diffuse, multivessel disease of calcified, tortuous arteries is more likely. As with many diseases in older people there may be more to gain but more risk.

Women

Women presenting with NSTE-ACS are older than men and have a higher frequency of diabetes, hypertension, heart failure, and other comorbidities.

Diabetes

Approximately 20–30% of patients with NSTE-ACS have known diabetes, and at least as many have undiagnosed diabetes or impaired glucose tolerance.

Renal disease

Renal dysfunction is present in 30–40% of patients with NSTE-ACS.

Heart failure

Heart failure is one of the most frequent and deadly complications of NSTE-ACS.

Extreme body weight

Low body weight is associated with an increased risk of death, particularly of bleeding, frequently owing to inappropriate dosing of drugs. Obese patients have more risk factors, but are younger and more likely to receive evidence-based therapies and paradoxically may have better outcomes.

Non-obstructed coronary arteries

The pathophysiology of NSTE-ACS is not homogeneous and possible mechanisms include: a coronary artery spasm (Prinzmetal's angina), an intramural plaque complicated by acute thrombosis with subsequent recanalisation, coronary emboli and 'syndrome X'.

Anaemia

Anaemia is associated with a worse prognosis (cardiovascular death, myocardial infarction, or recurrent ischaemia) across the spectrum of ACS.

Bleeding

Bleeding is the most frequent non-ischaemic complication in the management of NSTE-ACS.

Thrombocytopenia

Thrombocytopenia can occur during treatment of NSTE-ACS, defined as a decrease in platelet count to < 100 000/ml or a drop of 50% from baseline. Thrombocytopenia is considered moderate if the platelet count is between 20 000 and 50 000/ml, and severe if < 20 000/ml. In the ACS setting, the two main types of drug-induced thrombocytopenia are heparin-induced thrombocytopenia and GPIIb/IIIa receptor inhibitor-induced thrombocytopenia.

What is Takotsubo cardiomyopathy?

Also called stress-induced cardiomyopathy, apical ballooning or broken heart syndrome, Takotsubo cardiomyopathy was first described in Japan and is characterised by acute, reversible left ventricular dysfunction without obstructive coronary artery disease and usually resolves spontaneously over a period of weeks. The pathophysiology seems to include endocrine, hormonal, neuropsychological, and microvascular factors. The characteristic appearances seen on angiography are a ballooned apical segment and a hypercontractile basal portion of the left ventricle reminiscent of the traditional fishing pot used in Japan to trap octopus – 'tako-tsubo'. Once considered rare, it could possibly be responsible for 1–2% of admissions for ACS. It mainly affects post-menopausal women and may be triggered by psychological or physical stress. Typical ischaemic cardiac pain is the usual symptom, and the electrocardiogram may show ST elevation or negative T waves with QT prolongation. These ST segment changes may be widespread. The troponin level is usually slightly raised. Diagnosis requires coronary angiography to exclude obstructive coronary artery disease. Treatment is supportive, and prognosis generally good.

Why are patients with diabetes at higher risk of an ACS?

Diabetes is associated with risk factors for accelerated CVD and risk of ACS. These include a prothrombotic state mediated by increased plasminogen activator inhibitor 1 and increased GPIIbIIIa receptors, and increased endothelial dysfunction mediated by hyperglycaemia and dyslipidaemia. Whilst it is desirable to maintain blood glucose levels ≤ 11.1 mmol/l in an ACS, intensive glucose lowering has not been shown beneficial.

What are the immediate management principles in a STEMI?

In the absence of contraindications, reperfusion therapy should be instituted without delay if there is ST elevation, new left bundle branch block or evidence of posterior infarction. Either thrombolysis or primary percutaneous coronary intervention (PPCI) is acceptable, though PPCI is considerably preferable. 'Time is muscle'. Electrocardiogram criteria for thrombolysis (in the absence of a long list of contraindications) are 1 mm ST elevation in at least two contiguous leads or 2 mm ST elevation in at least two contiguous precordial leads or new left bundle branch block (or evidence of a posterior myocardial infarction). Advantages of PPCI include a higher patency rate of the artery, reduced short- and long-term mortality, reduced re-infarction and stroke rates, shorter hospital stay and likely cost effectiveness. Early PCI in cardiogenic shock is also beneficial.

Are there other causes of ST elevation?

Causes of ST elevation are listed in Box 2.30.

What do you know about right ventricular infarction (RVI)?

The V4R lead and other chest leads placed on the right side of the chest symmetrical to where they are usually placed may help diagnose RVI. V4R should be performed in the setting of an acute inferior territory infarct when it may reveal ST segment elevation that is absent in its usual V4 placement. RCA occlusion usually threatens the inferior wall of the heart. Unlike LAD territory, which supplies much of the anterior wall (scarring of which impairs left ventricular function), RCA territory supplies the atrioventricular node in 80% of cases (the circumflex artery supplying it in the remaining 20%) and RCA infarcts tend to cause bradyarrhythmias. Temporary pacing is often life saving but, because these arrhythmias often represent reversibly ischaemic penumbrae, long-term pacing is not inevitable. ST elevation in right-sided leads implies involvement of the right ventricular branch (RVB) of the

RCA. This occurs if the RCA occlusion is proximal to its RVB offshoot. An infarcted right ventricle will impair left heart filling and cause hypotension. Bradyarrhythmias will also cause hypotension, as will a more extensive infarct with left ventricular involvement, as will hypotensive drugs such as beta blockers. Unlike most causes of hypotension in the setting of acute myocardial infarction, RVI demands high filling pressures. Fluids, rather than diuretics, are needed to maintain right ventricular output and left ventricular filling.

Which complications may follow myocardial infarction?

These are listed in Box 2.31.

Box 2.30 **Causes of ST elevation**

- Normal in 90% of healthy young males – concave elevation 1–3 mm in V2 especially or early repolarisation marked in V4 with notching of the J point and tall upright Ts (+/– reciprocal ST depression aVR); some of these changes are sometimes referred to as high take-off
- Normal variant
- Left ventricular hypertrophy
- Left bundle branch block
- Pericarditis (diffuse)
- Hyperkalaemia
- Brugada syndrome
- Pulmonary embolism
- Cardioversion (transient)

What are the important secondary preventive measures after an ACS?

Secondary preventive measures are described in Table 2.19.

'Uncomplicated' patients may be discharged from hospital at day 5. Patients should mobilise at home for the following week, and gradually increase their exercise thereafter. Cardiac rehabilitation programmes are now well developed.

How might you investigate acute severe interscapular pain?

The three important diagnoses to exclude (the 'triple rule out') are myocardial infarction, pulmonary embolism and an acute aortic syndrome (aortic dissection or intramural haematoma). Correct diagnosis is imperative because of widely differing treatment options.

Box 2.31 **Complications of myocardial infarction**

- Arrhythmias (heart block especially in inferior infarction)
- Heart failure / acute pulmonary oedema (especially in anterior infarction)
- Papillary valve rupture and mitral regurgitation
- Septal rupture
- Thromboembolism (atrial fibrillation or mural thrombus)
- Pericarditis / Dressler's syndrome (pericarditis, pleurisy and pyrexia)

Table 2.19 Secondary preventive measures following an acute coronary syndrome

Treatment	Comment
Antiplatelet therapy (aspirin 75–150 mg daily)	Continued indefinitely unless contraindications (DAPT for 12 months after moderate to high-risk NSTEMI and at least 4 weeks after STEMI)
Beta blocker	Continued indefinitely unless contraindications
Statin	Continued indefinitely unless contraindications Intensive lipid lowering more beneficial than moderate (high-dose atorvastatin recommended for first few months at least)
ACE inhibitor	All patients indefinitely unless contraindications (angiotensin receptor blockers if intolerant) All should have echocardiogram to assess left ventricular function and exclude mural thrombus
Blood pressure, lipid and glycaemic targets	As for all patients at high cardiovascular disease risk
Rehabilitation	Mobilisation days 2–3, with risk factor modification, lifestyle assessment and introduction to cardiac rehabilitation
Aldosterone antagonists	All patients with left ventricular systolic dysfunction post myocardial infarction and diabetes or heart failure without significant renal impairment or hyperkalaemia, after institution of beta blocker and ACE inhibitor (from day 3–14) indefinitely (spironolactone greatest evidence in heart failure, eplerenone evidence post myocardial infarction)
Anticoagulation	Considered for patients with atrial fibrillation, large anterior wall myocardial infarction, severe left ventricular dysfunction or echocardiographic evidence of mural thrombus or left ventricular aneurysm
Implantable cardiac defibrillator	Considered for patients at risk of sudden cardiac death Antiarrhythmic drugs other than beta blockers exhibit harm or no benefit

ACE, angiotensin-converting enzyme; DAPT, dual antiplatelet therapy; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.

Serial electrocardiogram and 12-hour troponin testing

This has a high accuracy for ruling in or out an ACS but does not inform about pulmonary embolism or aortic dissection.

Echocardiography

Transthoracic echocardiography does not adequately visualise the distal ascending, transverse or descending aorta and has only 60% sensitivity and 30% specificity for detecting aortic dissection. Transoesophageal echocardiography improves these detection rates to 97–99% and 77–85%, respectively, because of the close proximity of the oesophagus to the thoracic aorta, but carries a 2% complication rate (bacteraemia, oesophageal rupture, bleeding). It can only detect the haemodynamic consequences of obstructive embolism such as increased right ventricular size, flattening of the interventricular septum and tricuspid regurgitation, present in only 30–40% of patients. It has high sensitivity for detecting wall motion defects following myocardial infarction but low specificity.

Electrocardiogram gated multidetector CT

Performed in late diastole when the heart is relatively static, this informs about the heart, lungs and pulmonary vasculature, and great vessels in a single study. Sensitivity and specificity for atheromatous coronary disease are 80–99% and 97%, respectively, and after myocardial infarction it will detect occlusion and the corresponding perfusion defect. Multidetector CT is the imaging modality of choice for an acute aortic syndrome, usually more readily available and less invasive than transoesophageal echocardiography, and detects a dissection flap or intramural haematoma with 83–98% sensitivity and 87–100% specificity; additional electrocardiogram gating improves image quality and allows coronary artery analysis. This investigation is also very sensitive in detecting pulmonary embolism; the sensitivity and specificity of CT pulmonary angiography for pulmonary embolism are 90% and 95%, respectively. This test is thus optimal for excluding the three important diagnoses in selected patients.

What do you know about aortic dissection?

Aortic dissection is caused by an intimal and medial tear in the aorta with propagation of a false lumen within the aortic media. It is part of the 'acute aortic syndrome' – an umbrella term for aortic dissection, intramural haematoma, and symptomatic aortic ulcer. Acute dissection is the most common aortic emergency, with an annual incidence of 3–4 per 100 000 in the UK, which exceeds that of ruptured aneurysm. The prognosis is grave, with 20% pre-admission mortality and 30% in-hospital mortality. Aortic dissection is categorised according to the time between the onset of symptoms and diagnosis and the site of the entry tear. A dissection is considered acute when diagnosis is made within 14 days of onset, and thereafter chronic. The location of the entry tear plays a key role in treatment and outcome, and it is classified by being in the ascending aorta (Stanford type A dissection) or distal to the origin of the left subclavian artery (Stanford type B dissection). Type A dissection carries a far worse prognosis than type B dissection and urgent surgical intervention is often needed. By contrast, acute type B dissection is usually managed conservatively if uncomplicated and surgically if complicated.

Causes

The causes of aortic dissection are multifactorial, with both inherited susceptibility and acquired degenerative disease.

White men aged over 40 years with hypertension, or those under 40 with Marfan syndrome or bicuspid aortic valves, are at highest risk.

Systemic hypertension is one of the most important risk factors, along with male sex and being white. Various connective tissue diseases predispose to the inherent weakening of the aortic wall and subsequent dissection, these diseases especially important in patients under 40 years, and include Marfan syndrome with fibrillin defects, Ehlers–Danlos type IV with abnormal synthesis of type III procollagen, and other connective tissue disorders associated with cystic medial necrosis. Congenital cardiovascular abnormalities such as bicuspid aortic valve increase the risk.

Presentation

Patients typically present with the abrupt onset of sharp tearing or stabbing chest pain, which may improve slightly over time, but pain may be absent in 10% of patients. Asymptomatic presentation is more common in diabetes. The pain may radiate to the neck in type A dissection or to the interscapular area in type B aortic dissection. Acute rupture or inadequate perfusion may cause a patient to become unconscious. Interrupted perfusion may result in neurological deficits, symptomatic limb ischaemia, or visceral ischaemia. Many differential diagnoses exist, including, for acute chest pain, an ACS, pulmonary embolism or spontaneous pneumothorax.

Management

The emergency management of patients with suspected aortic dissection is largely resuscitative, aiming for a heart rate of 60–80 beats/min and systolic blood pressure of 100–120 mmHg. A careful balance must be maintained between suppressing tachycardia and hypertension and ensuring adequate end-organ perfusion (monitoring urine output, mental and neurological state and peripheral vascular status). Twelve-lead electrocardiography is essential to exclude an ACS in the context of a potential aortic dissection.

CT aortography is the first-line diagnostic investigation, followed by transoesophageal echocardiography; magnetic resonance angiography is preferred for surveillance.

Management of a proximal (type A) dissection is surgically if possible. Uncomplicated distal (type B) dissection is best managed with intensive drug treatment; complicated type B dissection requires surgical intervention. All patients need lifelong antihypertensive therapy and surveillance imaging.

CASE 2.10 HEART FAILURE

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Julie Havelock, aged 78 years
> This lady has become increasingly dyspnoeic over the last 6 months. She has no cough. She has been sleeping with extra pillows for 2 months and her exertional tolerance has worsened. She gets occasional angina, relieved with a GTN spray. Her full blood picture, urea and electrolytes, glucose and liver and thyroid function tests are normal. Creatinine is slightly elevated at 128 mol/l and total cholesterol is 5.3 mmol/l. She takes aspirin, furosemide 40 mg daily and ramipril 5 mg daily. I would appreciate your further assessment.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Julie Havelock is a 78-year-old woman whose main symptomatic problem is shortness of breath. This has been progressive over the past 6 months, initially just on exertion but now she feels breathless lying in bed without three pillows. She has found it increasingly difficult to walk to the shops over the past 6 months. She gets very occasional angina on exertion that is rapidly relieved with a spray. This is a problem for her because she does not drive on account of visual impairment from age-related macular degeneration and her husband, who is 10 years older than she, suffers from dementia. She is his main carer. They live in a house with stairs, which she still manages to climb. She has never smoked, but has a family history of 'heart trouble'. There is a parrot at home, which they have had for 4 years. She is otherwise well but takes a substantial amount of ibuprofen for long-standing back pain.

How to approach the case

Data gathering in the interview and interpretation and use of data gathered

Presenting problem(s) and symptom exploration

■ **Elicit details of symptoms.** Try to confirm that symptoms are consistent with heart failure rather than other common causes of dyspnoea such as chronic obstructive pulmonary disease (COPD), recurrent pulmonary emboli, lower respiratory tract infection and pleural effusion/malignancy. Left ventricular systolic dysfunction (LVSD) on an echocardiogram does not exclude alternative causes or the possibility of multiple causes of breathlessness. Hypoalbuminaemia due to liver disease (impaired synthesis) or renal disease (e.g. nephrotic syndrome), lower limb venous insufficiency and drug-induced fluid retention (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), dihydropyridine calcium channel blockers causing ankle swelling) may also masquerade as heart failure. Renal artery stenosis may cause 'flash floods' of pulmonary oedema.

Left ventricular failure (LVF) may result in dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, nocturnal cough or fatigue (signs include a third heart sound, tachycardia, hypotension, bibasal crackles). Remember that symptoms that are worse when lying flat do not necessarily imply LVF. Symptoms from gastro-oesophageal reflux disease, post-nasal drip and bronchial secretions can also be worse supine.

Right ventricular failure may result in ankle swelling (signs include raised jugular venous pulse, pulsatile tender hepatomegaly, sacral and peripheral oedema).

Biventricular failure leads to both sets of symptoms.

■ **Establish symptom severity.** The New York Heart Association (NYHA) classification is summarised in Box 2.32.

■ **Consider causes.** There are many causes of heart failure, although the usual is ischaemic heart disease (Table 2.20).

Box 2.32 **New York Heart Association classification of heart failure symptoms**

- I – no limitations
- II – slight limitation of physical activity
- III – marked limitation of physical activity
- IV – symptoms at rest

Table 2.20 Causes of heart failure

Causes		What to ask about
Ischaemic heart disease		Symptoms of angina Risk factors
Pressure overload, especially due to hypertension or aortic stenosis		High blood pressure Known valve disease
Volume overload, especially due to aortic or mitral regurgitation		Known valve disease
Arrhythmias, especially atrial fibrillation		Palpitations
Cor pulmonale (right heart failure secondary to lung disease)	COPD	Breathlessness on exertion and other respiratory symptoms
	Parenchymal lung disease	
	Pulmonary emboli (recurrent multiple pulmonary emboli remain underdiagnosed)	
Cardiomyopathy	Hypertrophic cardiomyopathy	Ask if history suggests a possibility, e.g. alcohol
	Dilated cardiomyopathy, e.g. alcohol, haemochromatosis, diabetes	
	Restrictive cardiomyopathy, e.g. sarcoid, amyloid	
Myocarditis		Ask if history suggests a possibility, e.g. viral illness before symptoms, chemotherapy drugs
Pericardial disease		Ask if history suggests a possibility, e.g. viral illness, tuberculous, connective tissue disease, malignancy
High output failure		Ask if history suggests a possibility, e.g. thyrotoxicosis, anaemia, Paget's disease, left-to-right cardiac shunts

COPD, chronic obstructive pulmonary disease.

Patient perspective

Explore her thoughts about the cause of symptoms and her expectations of treatment. What can she no longer do that she would like to do? The impact on the care for her husband is paramount.

Past medical history

This usually unveils some cardiovascular risk factors.

Drug and allergy history

Ask about NSAIDS.

Family history

It is unlikely that this is relevant in this case.

Social history

Exploring support from family, and any need for and her willingness to accept adjunctive support from social services, occupational therapy (e.g. stairlifts) and of course her GP is pivotal, as is a predictive approach to future care pathways for her husband, with the support of her GP, and possibly community psychiatric services.

SUMMARY BOX – ASSESSMENT AND PLAN

- Patients with suspected heart failure and previous myocardial infarction should have transthoracic Doppler two-dimensional echocardiography and specialist assessment.
- Patients with suspected heart failure without previous myocardial infarction should have measured serum natriuretic peptide (B-type natriuretic peptide or *N*-terminal pro-B-type natriuretic peptide) levels. If the B-type natriuretic peptide level is > 400 pg / ml (116 pmol / l) or *N*-terminal pro-B-type natriuretic peptide level is > 2000 pg / ml (236 pmol / l), urgent echocardiography and specialist assessment are needed as very high levels of serum natriuretic peptides carry a poor prognosis. If the B-type natriuretic peptide level is 100–400 pg / ml (29–116 pmol / l), or *N*-terminal pro-B-type natriuretic peptide level is 400–2000 pg / ml (47–236 pmol / l), echocardiography and specialist assessment are warranted soon. If levels are less than these a diagnosis of heart failure is unlikely in an untreated patient.
- Situations that may reduce serum natriuretic peptide levels include obesity or treatment with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or aldosterone antagonists. Conditions other than heart failure that may raise serum natriuretic peptide levels include diabetes, sepsis, age > 70 years, and those affecting the heart (left ventricular hypertrophy, myocardial

ischaemia, tachycardia, right ventricular overload), the lungs (hypoxaemia – from causes including pulmonary embolism and chronic obstructive pulmonary disease), the kidneys (glomerular filtration rate < 60 ml/min) and the liver (cirrhosis).

- Electrocardiography and tests to evaluate possible aggravating factors and/or alternative diagnoses are important including chest radiography, pulmonary function tests, urine analysis, and blood tests for full blood count and film plus biochemical assessment of the liver, kidneys, thyroid, glucose, and lipids.
- Once heart failure has been diagnosed, severity, aetiology, precipitating factors and type of cardiac dysfunction (whether it is associated with left ventricular systolic dysfunction or preserved left ventricular ejection fraction) are important.

Discussion

What is heart failure?

Heart failure is a complex syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the heart to act as a pump to support physiological circulation, and is characterised by symptoms such as breathlessness and fatigue and signs such as fluid retention. Chronic heart failure affects over 1% of people in the UK, almost a million, with a prevalence of about 6–10% in people aged over 65 years, and overall prevalence is increasing. It carries a high morbidity and a 10% annual mortality. About a third of patients have a left ventricular ejection fraction (LVEF) ≤ 35%, up to 40% of whom are at risk of more severe heart failure and worse outcomes identified by conduction delay (QRS duration on a surface electrocardiogram of > 120 milliseconds).

What is the pathophysiology of heart failure?

The shape of the normal left ventricle is designed for maximal efficiency of ejection. Remodelling from scarring, hypertrophy (pressure overload) and dilatation (volume overload) compromises this ideal shape, and ushers in a vicious cycle of decreased cardiac output and compensatory neurohumoral stimulation (sympathetic nervous system and the renin–angiotensin–aldosterone system; RAAS) with positive ionotropy, salt and water retention and vasoconstriction. This leads to increased myocardial work, relative hypoxia, cell death and further left ventricular dysfunction. Arrhythmias are more likely.

What are the two main types of heart failure?

The two main types of heart failure are left ventricular systolic dysfunction or heart failure with reduced ejection fraction (HF-REF) and heart failure with preserved ejection fraction (HF-PEF). HF-PEF may be as common as HF-REF. Both types have a poor prognosis, although the introduction of effective treatments has led to a fall in mortality from heart failure caused by left ventricular systolic dysfunction (from 26% at 6 months in 1995 to 14% at 6 months in 2005). Diastolic heart failure is a term often used synonymously with HF-PEF, although they are not necessarily the same, and most patients with diastolic heart failure have some systolic dysfunction, too. HF-PEF refers to people with symptoms or signs of heart failure, a LVEF of > 50% and evidence of diastolic dysfunction (biomarkers, catheter evidence). The typical patient is female, elderly, overweight and hypertensive. The pathophysiology of HF-PEF is myocyte hypertrophy and fibrosis and a failure of or resistance to ventricular filling. A stiff ventricle causes compensatory atrial hypertrophy with a fourth heart sound (S4). The pathophysiology is more complex than mere diastolic dysfunction. In the normal heart, left ventricular twist during systole (which stores energy), motion of the mitral annulus towards the apex during systole (which also helps suck blood into the atrium) and the corresponding untwisting process and recoil in early diastole when that energy is released to generate the negative intraventricular pressure gradient or suction in early diastole are tightly coordinated. In patients with HF-PEF this coordination is disrupted, especially on exercise. A comparison of systolic and diastolic heart failure is given in Table 2.21.

Which pharmacological treatments improve the prognosis in heart failure?

Optimal treatments (Box 2.33) serve to modulate the RAAS and upregulate or re-sensitise β-receptors.

How do angiotensin-converting enzyme (ACE) inhibitors work?

ACE inhibitors inhibit ACE, which converts angiotensin I to angiotensin II (AII). AII has numerous actions including systemic vasoconstriction and stimulation of aldosterone. ACE inhibitors promote systemic vasodilation, which reduces afterload and preload. This reduces intracardiac pressures and unfavourable ventricular remodelling. Formerly, the combination of nitrates and hydralazine was used to respectively reduce preload and afterload.

Why are ACE inhibitors relatively contraindicated in aortic stenosis?

Reducing afterload increases the pressure drop or gradient across the aortic valve. Reducing preload limits the heart's capacity to compensate by increased cardiac output. Nitrates are thus also contraindicated in aortic stenosis, and antihypertensives other than ACE inhibitors/angiotensin receptor blockers (ARBs) such as calcium channel blockers need to be used with caution.

Why are ACE inhibitors relatively contraindicated in renal artery stenosis?

Numerous molecules act on the afferent and efferent arterioles in the kidney to maintain glomerular filtration rate. AII is activated by reduction in renal artery perfusion

Table 2.21 Comparison of systolic and diastolic heart failure

	Heart failure – reduced ejection fraction (HF-REF) – systolic heart failure	**Heart failure – preserved ejection fraction (HF-PEF) including diastolic dysfunction**
Demographics	Frequently male, typically elderly	Frequently female, usually elderly
LV ejection fraction	Reduced	Normal
LV cavity size	Usually dilated	Usually normal
LV hypertrophy	Sometimes hypertrophy	Usually concentric hypertrophy
Gallop rhythm	S3	S4
Causes / associations	Typically due to ischaemic heart disease with associated risk factors	As for systolic heart failure, but associated especially with left ventricular hypertrophy (hypertension; aortic stenosis), hypertrophic cardiomyopathy, restrictive cardiomyopathy, obesity, chronic lung disease, sleep apnoea and long-term dialysis

LV, left ventricular.

Box 2.33 Pharmacological treatments in heart failure

Loop diuretics

Everyday experience shows that these improve symptoms but there is no evidence for prognostic improvement. They are used for patients with signs of salt/water retention at any stage in the concomitant therapeutic ladder and as first-line therapy in patients with acute pulmonary oedema. Bumetanide 1 mg is approximately equivalent to furosemide 40 mg, and may be metabolically 'cleaner' with a lower risk of gout and glucose disturbance. A thiazide such as metolazone for short-term use (days) may aid large-volume fluid loss as adjunctive treatment but often with significant metabolic derangement.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

ACE inhibitors improve outcome and should be used in all patients unless there are contraindications (e.g. significant renal impairment or renal artery stenosis). ARBs may be alternatives for patients intolerant of ACE inhibitors. The combination of nitrates and hydralazine remains an alternative for the few patients intolerant of both. ACE inhibitors should be started at low dose and titrated upwards (e.g. at 2-weekly intervals) to the target dose provided blood pressure and chemistry allow. Asymptomatic hypotension is usually acceptable if systolic blood pressure is above, say, 90–100 mmHg, and symptomatic hypotension may be limited by limiting the use of other vasodilating antihypertensives. Cough occurs in about one-third of patients. A rise in urea, creatinine and potassium is to be expected. A rise in creatinine to 50% above baseline or to 200 μmol/l, whichever is smaller, is acceptable. A rise in potassium to ≤ 5.9 mmol/l is acceptable. Other potentially nephrotoxic drugs should be limited. If greater rises in creatinine or potassium occur the dose of the ACE inhibitor should be halved and stopped if subsequent chemistry shows an unsatisfactory response, and the ACE inhibitor should be stopped without further ado if creatinine rises by > 100% or to 350 μmol/l or potassium to 6.0 mmol/l and chemistry should be monitored until stable.

Beta blockers

These improve outcome in patients who have already been treated with an ACE inhibitor but negative ionotropism has the potential for harm and treatment should only be considered in chronic, stable heart failure without clinical or radiological signs of decompensation. The rule is to 'start low and go slow'. Beta blockers may not improve symptoms despite improving prognosis, a fact that should be shared with patients. Bisoprolol starting at 1.25 mg titrating to a target of 10 mg once daily and carvedilol 3.125 mg twice daily titrated to 25 mg (50 mg if mild to moderate heart failure and > 85 kg) twice daily are licensed for treatment and metoprolol succinate also has an evidence base in heart failure. Doses should be doubled at not less than 2-weekly intervals, carefully monitoring heart rate, blood pressure and fluid status. If heart rate is < 50 beats per minute the dose should be halved and if more severe deterioration occurs the drug should be stopped. Drugs that compound bradycardia, such as digoxin or amiodarone, should be used with caution and rate-limiting calcium channel blockers are virtually contraindicated. Rebound worsening of ischaemia or arrhythmias may occur with beta-blocker withdrawal. Ivabradine an alternative rate control agent, has an emerging place in heart failure (SHIFT trial).

Aldosterone antagonists

Low-dose spironolactone (25 mg, titrated to 50 mg) should be considered for patients who remain moderately to severely symptomatic in New York Heart Association (NYHA) class III–IV despite optimal therapy, with careful monitoring of blood chemistry because the combination with ACE inhibitors or ARBs can lead to dangerous hyperkalaemia. If potassium rises to ≥ 6.0 mmol/l or creatinine to > 200 μmol/l spironolactone should be stopped. Breast discomfort or gynaecomastia are potential complications. Eplerenone is beneficial in stable patients with left ventricular ejection fraction ≤ 40% and clinical evidence of heart failure after recent myocardial infarction.

Digoxin

This should be considered in all patients with heart failure and atrial fibrillation and in patients in sinus rhythm who are symptomatic despite optimal therapy. There is no significant evidence of a survival benefit, but it may reduce hospital admissions.

Antiplatelet and statin therapy

These are indicated if there is concomitant atherosclerotic arterial disease. There is no evidence for antiplatelet therapy otherwise in

Box 2.33 **Pharmacological treatments in heart failure—cont'd**

heart failure, and the WATCH study examined aspirin, clopidogrel and warfarin in such patients and failed to find significant differences in endpoints other than a trend favouring warfarin in non-fatal stroke. Heart failure patients were excluded from many statin trials, and there is no evidence for statin use in heart failure, and indeed some data even suggest that cholesterol may be beneficial, perhaps by mopping up endotoxin. This illustrates the dangers of extrapolating results from trials to different populations.

Anticoagulation

This is indicated in atrial fibrillation and in sinus rhythm with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus.

Practical recommendations (National Institute for Health and Clinical Excellence guidance)

Heart failure with reduced ejection fraction

ACE inhibitors and beta blockers licensed for heart failure should be offered to all patients with heart failure caused by left ventricular systolic dysfunction. For beta blockers, this includes older adults as well as patients with peripheral vascular disease, erectile dysfunction, diabetes mellitus, interstitial pulmonary disease, or chronic obstructive pulmonary disease without reversibility. For patients who have intolerable side effects with ACE inhibitors, an ARB licensed for heart failure is an alternative. For patients intolerant of both ACE inhibitors and ARBs, hydralazine in combination with a nitrate may be considered.

If a patient remains symptomatic despite optimal treatment with an ACE inhibitor and a beta blocker, second-line treatment may be considered: an aldosterone antagonist licensed for heart failure, especially in moderate to severe heart failure (NYHA class III or IV) or if there has been a myocardial infarction within the past month; or an ARB licensed for heart failure, especially in mild to moderate heart failure (NYHA class II or III); or hydralazine in combination with nitrate (especially if the patient is of African or Caribbean descent with moderate to severe heart failure (NYHA class III or IV).

Digoxin may be considered for worsening or severe heart failure caused by left ventricular systolic dysfunction despite first-line and second-line treatment.

Heart failure with preserved ejection fraction

Treatment of congestive symptoms is with diuretics, alongside optimal management of comorbidities such as hypertension, ischaemic heart disease and diabetes. Insufficient evidence exists to recommend on the role of ACE inhibitors, ARBs, and beta blockers.

pressure, via the RAAS. AII promotes renal vasoconstriction (of the afferent and efferent arterioles, the efferent arteriole being especially important because it constricts to maintain intraglomerular pressure). ACE inhibitors (and ARBs) promote afferent and efferent arteriole vasodilation. In renal artery stenosis, the efferent arteriole dilates increasing 'run-off' in the setting of a reduced afferent supply. Blood effectively bypasses the glomerulus. This concept is explained more fully in Case 2.26.

When might you suspect renal artery stenosis clinically?

The presence of a renal bruit (epigastric or loin) is helpful. Peripheral vascular disease may be surrogate evidence.

How do ARBs work?

ACE inhibitors effectively act as a 'dam' to the production of AII, which gives rise to two potential problems:

1. Accumulation of substrates such as bradykinin, which promote cough, potential angioedema and other side effects (it is unclear whether all substrates which build up are potentially harmful or whether indeed some may confer benefit)
2. Alternative ways 'around the dam' to promote AII.

ARBs provide a molecular spanner limiting the effects of AII. However, numerous AII receptor sites have been identified in humans, including AT_1 and AT_2. Blocking AT_1 appears to be important in treating heart failure, whereas AT_2 may have important endothelial roles whose blockade may be best avoided. Selective ARBs may be developed in future. ACE inhibitors and ARBs may be used in combination, but with beta blockers the triple combination is potentially dangerous.

Should ACE inhibitors and ARBs be used in combination?

The CHARM study programme of 7601 patients using candesartan compared with placebo in a broad range of patients with heart failure irrespective of systolic function or background therapy had three facets. In CHARM Alternative (LVEF ≥ 40%, patients intolerant of ACE inhibitors) there was unequivocal risk reduction in cardiovascular death or hospitalisation from heart failure. In CHARM Added (LVEF ≥ 40%, patients on ACE inhibitors for at least 30 days) there was a small but significant risk reduction in cardiovascular death or hospitalisation from heart failure, but no effect on all-cause mortality. Benefit was also seen in patients taking a beta blocker, contrasting with previous data suggesting that the triple combination of ACE inhibitor, ARB and beta blocker was associated with adverse outcomes. In CHARM Preserved (LVEF ≥ 40%, history of hospitalisation for a cardiac reason with or without current use of ACE inhibitor) there was a trend towards reduction in cardiovascular death or hospitalisation from heart failure. There is general consensus that ARBs should be used in heart failure in patients intolerant of ACE inhibitors but combination therapy is not without debate.

How do beta blockers work in heart failure?

Beta blockers reduce sympathetic drive on the heart. In chronic heart failure, cardiac β-receptors are down-regulated, but β_2-receptors to a lesser extent than β_1. It might, therefore, be that β_2-receptors are relatively more active in heart failure than in the normal heart, and that non-selective beta blockers are preferable to β_1-selective drugs. The Carvedilol Or Metoprolol European Trial (COMET) compared metoprolol (a beta$_1$-selective blocker) with carvedilol (a non-specific beta blocker that blocks both β_1 and β_2 and that has alpha-blocking effects). Carvedilol produced a striking reduction in all-cause mortality, favouring non-selective blockade, but there has been concern that the dose and formulation of metoprolol used in COMET was different from that in the MERIT-HF study, which showed the benefit of metoprolol. Bisoprolol is a selective beta$_1$-blocker. One should never assume class effects, and current evidence favours bisoprolol (highly cardioselective) or carvedilol (not cardioselctive and produces significant peripheral vasodilation) in heart failure.

How does spironolactone work in heart failure?

Spironolactone inhibits aldosterone but also seems to reduce cardiac filling pressures and stiffness and enhance compliance. The RALES trial demonstrated the benefit of spironolactone in heart failure and EPHESUS showed that eplerenone improved outcome in LVSD following myocardial infarction.

List some non-pharmacological interventions you might consider for a patient with heart failure

- Management of other modifiable risk factors (smoking cessation, hypertension, diabetes)
- Stopping drugs which precipitate fluid retention (e.g. NSAIDs, corticosteroids, calcium channel blockers) or depress myocardial function
- Salt restriction (ready-to-cook meals and convenience foods have a high salt content)
- Fluid intake restriction to 1.5–2 litres daily in advanced heart failure
- Exercise and cardiac rehabilitation programme
- Weight reduction (unless cardiac cachexia)
- Vaccination (influenza annually, pneumonococcal once only)

The role of coronary artery bypass grafting revascularisation in patients with heart failure from coronary disease is uncertain, and the HEART-UK study aims to further inform in the setting of angina and heart failure. Underlying precipitants such as anaemia may need to be corrected. Heart failure is frequently associated with anaemia of chronic disease.

What do you know about devices in heart failure?

Cardiac resynchronisation therapy (CRT), also known as biventricular pacing, can overcome the dyssynchrony resulting from left bundle branch block (LBBB) and subsequently improve cardiac output in the failing heart. Despite numerous imaging studies, LBBB on the 12-lead electrocardiogram is still the best way to identify patients who may respond to CRT. Implantable cardioverter defibrillators (ICDs) prevent sudden cardiac death from ventricular arrhythmias and prolong life in specific subgroups of patients.

Cardiac resynchronisation therapy (CRT)

Conduction system disease is common in heart failure, identified by a broad QRS complex and accompanied by dyssynchronous, inefficient cardiac contraction, increased mitral regurgitation, and regional ischaemia, all contributing to further adverse remodelling and worsening cardiac function. Around 20% of patients with heart failure have LBBB, resulting in desynchronisation of left ventricular systolic contraction (left ventricular dyssynchrony) because of delayed contraction of the posterior left ventricle relative to the septum. CRT is an effective treatment for heart failure with LVSD and conduction delay, and can reduce symptoms and admission to hospital and improve quality of life and prognosis.

How CRT works

CRT is a form of cardiac pacing that improves coordination of the atria and both ventricles. The device is similar to a conventional dual-chamber pacemaker but has an additional ventricular lead. Pacing leads are placed through the subclavian vein into the right atrial appendage, at the right ventricular apex (the anterior wall of the left ventricle) and into the left ventricular posterolateral free wall (via a tributary of the coronary sinus). The leads are connected to a subcutaneous generator programmed to deliver simultaneous right and left ventricular pacing (with simultaneous pacing of the septum and left ventricular free wall) in response to each sensed sinus beat. Pacing both sides of the left ventricle improves coordination of left (and right) ventricular contraction and cardiac output, reduces mitral regurgitation during rest and exercise, and improves regional perfusion defects. To override intrinsic conduction, the atrioventricular delay is set shorter than the intrinsic PR interval. In selected patients CRT is combined with protection from sudden cardiac death with an ICD.

Patient selection

Improvement in symptoms was experienced by 60–70% of patients with heart failure and LBBB after CRT. The best predictor of symptomatic response remains an electrocardiogram showing a QRS duration of ≥ 120 milliseconds. Evidence (from numerous studies including CARE-HF) is clear that mortality and morbidity outcomes are improved, too, such that a failure to improve symptomatically after CRT does not imply failure to respond. Whether those with a shorter QRS duration (< 120 milliseconds) benefit remains unclear. American and European guidelines recommend CRT for patients with NYHA classes III and IV heart failure, an ejection fraction $\leq 35\%$ and QRS duration of ≥ 120 milliseconds. National Institute for Health and Clinical Excellence (NICE) guidelines recommended CRT with a pacing device (CRT-P) as a treatment option for people with heart failure who fulfil all the following criteria:

- Experiencing or have recently experienced NYHA class III–IV symptoms
- In sinus rhythm – *either* with a QRS duration of 150 milliseconds or longer *or* with a QRS duration of 120–149 milliseconds and mechanical dyssynchrony confirmed by echocardiography
- LVEF ≤ 35%
- Receiving optimal pharmacological therapy.

CRT with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device. Those with atrial fibrillation probably benefit as much provided that intrinsic conduction is suppressed pharmacologically or by atrioventricular node ablation. Guidelines do not distinguish between patients with right and left bundle branch block, both of whom may be considered for biventricular pacing. Age is unrelated to outcomes from heart failure treatments, including CRT, but is related to outcomes from ICDs.

Implantable cardioverter defibrillator (ICD)

The use of ICDs in ischaemic heart disease and severe heart failure without a previous arrhythmic event (primary prevention) remains controversial. Evidence suggests mortality benefit only in those with mild heart failure (NYHA class I or II). ICDs are recommended by NICE in the following situations.

Secondary prevention

For patients who present, in the absence of a treatable cause, with one of:

- Having survived cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation (VF)
- Spontaneous sustained VT causing syncope or haemodynamic compromise
- Sustained VT without syncope or cardiac arrest, and an associated reduction in ejection fraction (LVEF < 35%) (no worse than NYHA class III).

Primary prevention

- For patients who have a history of previous (more than 4 weeks) myocardial infarction and *either* an LVEF < 35% (no worse than NYHA class III) and non-sustained VT on electrocardiogram monitoring and inducible VT on electrophysiological testing *or* LVEF of < 30% (no worse than NYHA class III) and QRS duration ≥ 120 ms.

NICE guidelines for CRT and ICDs therefore overlap only in patients with class III heart failure, although many cardiologists think a single procedure sensible in patients with class II symptoms as many will deteriorate. An ICD in class III symptoms may reduce sudden death but there is increased mortality from heart failure, and ICDs are also associated with a higher complication rate than CRT alone, including inappropriate discharges, and so those with class III symptoms, those aged over 75 years, and those with very poor ventricular function (< 10%) should be considered very carefully. In non-ischaemic cardiomyopathy the evidence is neutral for the benefit of ICDs.

What do you know about surgery in heart failure?

In Western countries 70% of heart failure patients have coronary artery disease with transient ischaemic dysfunction, hibernating myocardium or scar. The remainder have hypertension, valvular heart disease or idiopathic dilated cardiomyopathy (DCM). Left ventricular shape and volume are important determinants of symptomatic status and outcome. Whilst LVEF alone is a poor predictor of survival in the presence of reversible ischaemia, the onset of mitral regurgitation portends a poor prognosis.

Surgery to vessels, valves and ventricle

Surgery addresses the three V's: vessels (obstructed coronary arteries), valve (mitral) and left ventricle (dyskinesia or scar). Revascularisation of hibernating myocardium can improve left ventricular function and longevity with outcomes superior to transplantation. The benefits of mitral repair and left ventricular remodelling are less certain. Aortic valve disease responds to conventional valve surgery and DCM patients with secondary mitral regurgitation may improve after valve repair. Surgery must be considered before comorbidity, such as renal dysfunction, substantially increases operative risk. In the presence of poor left ventricular function (LVEF 10–30%) hospital mortality can be avoided by elective deployment of an intra-aortic balloon pump or left ventricular assist device.

Transplantation and left ventricular assist devices (LVADs)

Donor hearts are a scarce commodity but mechanical blood pump bioengineering is improving. The observation that pulse pressure is of limited functional importance (compared with flow) has allowed the development of miniaturised continuous-flow devices for long-term use, whilst unloading (resting) the deteriorating left ventricle has been shown to reverse many cellular and molecular changes in heart failure promoting improvement in myocardial function. Temporary extracorporeal assist devices are used to salvage patients with cardiogenic shock after myocardial infarction, those with myocarditis and after surgery. Implantable LVADs are emerging as an alternative to transplantation. For ischaemic cardiomyopathy the combination of a LVAD with autologous or allogenic bone marrow stem cells to improve vascularity is being considered.

How might you differentiate between heart failure and cor pulmonale in a patient with significant peripheral oedema?

A history of COPD, a bounding pulse and warm peripheries favours the latter; heart failure is often associated with cool peripheries.

How would you define ‘acute’ heart failure and what are its causes?

This is not as easy as it may seem, given that heart failure is one of the most common medical discharge diagnoses. Heart failure, acute or chronic, has no universally agreed definition. The term ‘acute’ heart failure is often used to mean worsening breathlessness leading to breathlessness (at rest when sitting upright), synonymous with the term acute cardiogenic pulmonary oedema (ACPOE). Some suggest that the term ‘acute heart failure’ might be abandoned or should refer to new-onset heart failure regardless of its severity. The European Society of Cardiology proposed six subgroups of ‘acute’ patients: cardiogenic shock; hypertensive heart failure; heart failure with acute coronary syndrome; isolated right heart failure; worsening chronic heart failure; ACPOE. Many clinical trials have been tempered by tempestuous interpretation of definition. About two-thirds of patients have a prior diagnosis of heart failure. Many admissions reflect worsening in underlying heart function, but myocardial ischaemia, arrhythmias (especially atrial fibrillation), hypertension, sepsis, medication changes or excessive dietary salt or alcohol may all precipitate acute deterioration of chronic heart failure or cause new-onset heart failure. Probably only about 50% of cases are associated with a reduced LVEF.

What is the pathophysiology of ACPOE?

ACPOE reflects pulmonary venous (left atrial) hypertension. The precise left atrial pressure (LAP) at which ACPOE develops varies, dependent upon alveolar capillary membrane permeability, plasma oncotic pressure and the efficiency of pulmonary lymphatic drainage. Patients with chronic heart failure may be less likely to develop ACPOE at a given LAP because of hypertrophy and constriction of

Table 2.22. Managing acute cardiogenic pulmonary oedema (ACPOE)

Treatment	Rationale
Sit upright and give high-flow (60–100%) O_2 (caution in severe chronic respiratory disease)	ACPOE can lead to hypoxaemia, which in turn leads to pulmonary vasoconstriction, increasing the load on the right ventricle. However, overcorrection may provoke systemic vasoconstriction and could be harmful and there is no evidence that high-flow oxygen improves symptoms or outcome in ACPOE. It is routinely given as it anecdotally helps symptoms.
i.v. bolus diuretic: at least 40 mg furosemide or 1 mg bumetanide if diuretic naive or 80–120 mg if on chronic diuretic therapy; infusion if higher doses needed	There is inconclusive evidence of clinically worthwhile venodilator effects and preload reduction.
Diamorphine initially 2.5 mg (caution if severe respiratory disease) and metoclopramide (10 mg) i.v., repeated if needed	Opiates rapidly relieve distress and slow respiratory rate, and are coronary vasodilators, but there is little evidence for haemodynamic benefit.
Sublingual nitrate spray, followed by i.v. nitrate infusion, initially GTN 20 μg / min or ISD, initially 2 mg / h titrated up to 10-fold at 15-minute intervals (BP monitoring essential)	The evidence that vasodilators are safe and/or effective in ACPOE is not robust. Vasodilators, especially nitrates, may cause hypotension that can exacerbate myocardial perfusion deficits.
CPAP if exhaustion or failure to respond within 60 min *or* mechanical ventilation if failure to tolerate CPAP and need for ventilation	When high-flow oxygen is unable to correct hypoxaemia, NIV should be considered. NIV does not improve outcome but may improve symptoms not responding to first-line measures. If hypercapnia develops, the patient may require invasive ventilation unless there is a decision for palliative care, in which case sufficient morphine to relieve distress is warranted. Indications for invasive ventilation include exhaustion, hypoxaemia < 8 kPa, hypercapnia > 8 kPa, acidosis pH < 7.2 or failure to respond to NIV.
Circulatory support – an ominous sign, generally successful only as a bridge to a rescue procedure (surgery or percutaneous cardiac procedure)	There is no obvious role for inotropic agents in the management of ACPOE. If the patient is hypotensive and developing shock, the alternatives are reversing the underlying problem, usually by surgery or percutaneous intervention, or reverting to palliative care. There is no evidence that renal-dose dopamine is effective.
Atrial fibrillation: digoxin, 500 μg i.v. over 1 min, repeated if necessary; may be supplemented by amiodarone 450 mg i.v. bolus, ideally through a long line but peripherally provided no extravasation and flushed with normal saline, with further 300 mg after 30 min. i.v. esmolol may be considered, but no evidence base Myocardial ischaemia: consider nitrates, and perhaps cautious use of esmolol if tachycardia Myocardial infarction: revascularisation Patients should receive heparin prophylaxis for deep venous thrombosis or full dose heparin if in atrial fibrillation	

BP, blood pressure; CPAP, continuous positive airway pressure; GTN, glyceryl trinitrate; ISD, isosorbide dinitrate; i.v., intravenous; NIV, non-invasive ventilation.

precapillary arterioles, reduced alveolar capillary membrane permeability and increased lymphatic drainage. Increases in LAP may be due to fluid retention or fluid translocation. The former, but not the latter, is associated with weight gain and peripheral oedema. Sudden severe mitral regurgitation, severe myocardial ischaemia, atrial fibrillation with a rapid ventricular response or severe systemic hypertension associated with a stiff and hypertrophied left ventricle may all lead to pulmonary oedema without weight gain or obvious fluid retention.

How is 'acute heart failure' diagnosed?

The typical patient is pale, cool to touch and sweaty, reflecting intense sympathetic activation, obviously breathless and sitting upright clutching the bedrails. Coughing up pink frothy sputum is relatively uncommon. There may be central or peripheral cyanosis and reduced oxygen saturations. The venous pressure is often hard to determine. Most patients do not have peripheral oedema. Auscultation reveals bilateral fine basal pulmonary crackles that do not clear on coughing and there may be high-pitched expiratory wheeze.

A chest X-ray should exclude pulmonary causes of breathlessness and identify pulmonary oedema. An electrocardiogram will confirm heart rhythm and any evidence of conduction abnormalities, ventricular hypertrophy or myocardial ischaemia. Until recently the gold standard for confirming a diagnosis has been echocardiography showing a reduced LVEF. However, many people have all the features of heart failure, respond to treatment and yet have a normal LVEF. This appears to be a heterogeneous group of patients, for example those with rarer causes of heart failure such as constrictive pericarditis, those with paroxysmal disease (ischaemia or arrhythmia), those with a forme fruste of systolic dysfunction (long-axis dysfunction) and those with genuine diastolic dysfunction. There is also operator dependence.

Biomarkers, especially brain natriuretic peptide (BNP or NT-proBNP), may be helpful. Diagnosis can be refuted with some confidence if peptide levels are low. If levels are substantially elevated, the patient is in sinus rhythm and renal function not grossly abnormal, the diagnosis of acute heart failure may be made with confidence. Levels are increased in atrial fibrillation even in the absence of heart failure. Intermediate levels pose some uncertainty but some symptoms and signs combined with a modest elevation in levels most likely represent cardiac dysfunction, whereas severe symptoms combined with a slight elevation in levels suggest that the main diagnosis is not heart failure. BNP / NT-proBNP provides the best prognostic marker in heart failure.

How is ACPOE treated and what is the evidence for treatments?

The reason for ACPOE should be sought and managed. Many patients are hypertensive and have high LAPs but normal cardiac output. Treatment of ACPOE has changed little over the past few decades and conventional treatment is usually highly effective (Table 2.22).

CASE 2.11 PALPITATIONS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr Walter Cartwright, aged 74 years

Thank you for seeing this gentleman with a 2-month history of intermittent, fast palpitations. Episodes occur without warning, and during these he feels dizzy but has never lost consciousness. He has a history of ischaemic heart disease and I wonder if he is now describing paroxysmal atrial fibrillation. Past medical history comprises asbestosis with a mild restrictive picture (under annual review at the respiratory clinic) and giant cell arteritis diagnosed a year ago, under control on prednisolone 5 mg daily. He also takes aspirin, atenolol 50 mg daily (for infrequent angina), simvastatin 40 mg daily, alendronate and calcium / vitamin D. He lives with his wife and is an ex-smoker. On examination his heart rate is 44 beats per minute (his ECG shows sinus rhythm), blood pressure is satisfactory at 146 / 84, heart sounds are present with no murmurs and he has scattered chest crackles consistent with asbestosis. I would value your advice as to need for further investigation of his palpitations.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Walter Cartwright is a 74-year-old man who for the last 2 months has experienced episodes of fast, regular palpitations. He also experiences light-headedness, but has never lost consciousness. These differing episodes do not always occur together, and can occur at any time of day, at rest or during exercise. He has even been aware of symptoms in bed. He has a past medical history of chronic stable angina and asbestos-related lung disease with minor reduction in lung capacity. An ex-smoker of 40 cigarettes per day, he seldom drinks alcohol, takes moderate caffeine and is fully independent, living with his wife in their two-bedroom house. He has no real concerns and will be happy to be 'dismissed' without further tests.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Consider possible causes.** Palpitations are common, and many patients do not have a proven cardiac arrhythmia.

Older patients are more likely to have structural heart disease provoking atrial fibrillation (AF) or (non-sustained) ventricular tachycardia (VT). An older man with ischaemic heart disease and left ventricular dysfunction with intermittent fast, regular palpitations is more likely to have VT. Irregular palpitations may indicate AF. A 40-year-old woman with irregular, fast palpitations at rest and on exertion, who also feels sweaty, should be checked for thyrotoxicosis.

Younger patients are more likely to be describing sinus tachycardia or supraventricular tachycardia (SVT). Symptomatic ventricular ectopic beats (VEBs) are extremely common. Sinus tachycardia may be the result of anxiety, thyrotoxicosis, phaeochromocytoma or sympathomimetic drugs. A 30-year-old woman with fast, regular palpitations lasting several minutes to several hours is most probably describing SVT, and the baseline electrocardiogram may show evidence of Wolff–Parkinson–White (WPW) syndrome but will more likely be normal. Ambulatory electrocardiogram monitoring is indicated unless there is a clear precipitant such as caffeine or alcohol. A 25-year-old man with a history of feeling that his heart 'misses a beat', and whose episodes last a few seconds, often before falling asleep, is probably describing occasional ventricular or supraventricular ectopic beats, and can be reassured if there are no clinical signs of structural heart disease.

■ **Elicit details of the palpitations.** Ask:

- If these are regular (sinus tachycardia, SVT, VT) or irregular (AF, VEBs); patients can sometimes tap out the beat
- If these are fast (sinus tachycardia, AF, atrial flutter, SVT, VT) or slow
- If these are intermittent or persistent; if intermittent, ask about the frequency of attacks, abruptness of onset of each attack and duration of each attack
- For how long attacks have been recurring (since childhood suggests SVT)
- If there are any trigger or relieving factors such as exercise, caffeine, alcohol or drugs.

■ **Ask about associated symptoms.** Ask about chest pain, dyspnoea and syncope.

■ **Ask about risk factors for AF.** These include coronary heart disease, hypertension, valvular heart disease (history of rheumatic fever), alcohol intake and thyrotoxicosis.

Patient perspective

He may have no particular concerns, but that should not dissuade you from recognising that he could be describing tachyarrhythmias with or without significant sinus pauses, warranting an implantable cardiac defibrillator or pacemaker.

Past medical history

The history of ischaemic heart disease should alert you to episodes of AF or VT or a tachy–brady syndrome.

Drug and allergy history

Antihypertensive drugs, notably calcium channel blockers, may precipitate reflex tachycardia. Ask if any drug treatments have been tried for the palpitations.

Family history

This can be very relevant in younger patients with inherited structural heart disease (e.g. hypertrophic cardiomyopathy (HCM)) or an inherited conduction disturbance.

Social history

Explore the impact of his symptoms on his daily routine, notably driving.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ When palpitations are the primary symptoms, the most useful tests are a 12-lead electrocardiogram and electrocardiogram monitoring (exercise electrocardiogram testing if symptoms are produced on exercise). Echocardiography is unlikely to add information if clinical examination and the electrocardiogram are normal.
- ◆ This patient should have routine blood chemistry including potassium, magnesium and calcium levels, a 12-lead electrocardiogram and an ambulatory electrocardiogram recording (a patient-activated event recorder if episodes are sufficiently infrequent that 24–48-hour measurement is unlikely to capture any disturbance).
- ◆ He is likely to have sick sinus or 'tachy–brady' syndrome, ischaemic disturbance of the sinus node and its pathways. Presyncopal episodes are more likely to be the result of bradyarrhythmias than atrial fibrillation, although non-sustained ventricular tachycardia is a possibility. Sinus pauses of 3 or more seconds warrant a permanent pacemaker, as may shorter pauses that are symptomatic. Atenolol should be stopped, but if there is combined tachy–brady disturbance then beta blockers may be a necessary adjunct to a pacemaker.

Discussion

List some types of tachyarrhythmia

- AF
- Atrial flutter
- Atrial ectopy (focal / multifocal)
- Atrioventricular re-entry tachycardia (overt accessory pathway as in WPW syndrome / concealed accessory pathway)

- Atrioventricular nodal (junctional) re-entry tachycardia
- VT

How may SVT arise in WPW syndrome?

WPW syndrome is caused by an accessory conduction pathway that bypasses the atrioventricular node (AVN).

The accessory pathway may not always conduct and so the electrocardiogram may be intermittently normal. When it does conduct, impulses reach the ventricle from both the accessory pathway and the AVN. Impulses via the accessory pathway are faster than those through the AVN, giving rise to the delta wave on the electrocardiogram (pre-excitation). This does not usually provoke tachycardia.

There may, however, be retrograde conduction through the accessory pathway. This can arise during the transient window of opportunity when the accessory pathway is refractory (having delivered its impulses to the ventricle), and the slower AVN pathway is still conducting (an extrasystole is a common precursor, because it delays AVN conduction). At this time, AVN impulses may loop back up into the accessory pathway, setting up a loop of continuous conduction, which results in a re-entry SVT.

This antegrade conduction through the AVN and retrograde conduction through the accessory pathway is termed orthodromic conduction and produces a narrow complex tachycardia. Less commonly, conduction is down the accessory pathway, termed antedromic conduction, producing a broad complex tachycardia. These types of SVTs are referred to as atrioventricular re-entrant tachycardias.

How may SVT be treated?

Vagal manoeuvres (carotid sinus massage, Valsalva manoeuvre) or adenosine (3 mg then 6 mg then 12 mg) may terminate SVT by transiently blocking the AVN. Adenosine should be used with caution in chronic obstructive pulmonary disease and is contraindicated in asthma. Verapamil 5 mg intravenously over 1 minute, repeated once if necessary, is an alternative regimen. Beta blockers may be used.

Why is digoxin contraindicated in WPW syndrome?

AF occurs in up to 15% of patients with WPW. Digoxin must never be used because it decreases the refractory period of the accessory pathway and allows rapid antegrade conduction from atrium to ventricle. The very fast ventricular rate may degenerate to ventricular fibrillation.

What other types of SVT are there?

The AVN itself may contain both a slow and fast pathway and other SVTs may arise through the ability of the AVN to conduct in an antegrade direction down one of these and a retrograde direction along the other, giving rise to atrioventricular nodal re-entry tachycardias (AVNRTs). SVT is common in patients without structural aberrations in whom there may be numerous triggers such as caffeine or alcohol.

Which clinical or electrocardiographic features can help to determine whether a broad complex tachycardia is the result of VT or SVT with aberrant conduction?

VT is suggested by:

- History of ischaemic heart disease (the strongest predictive factor)
- QRS > 140 milliseconds
- Capture or fusion beats (intermittent sinoatrial beats, or sinoatrial beats fused with ventricular beats)
- Concordance in precordial leads (all of the V lead complexes point in the same direction)
- Absence of bundle branch block on a previous electrocardiogram in sinus rhythm.

How might you manage VT?

Drug therapy for ventricular arrhythmias is limited by the pro-arrhythmic potential of antiarrhythmic drugs. Monomorphic VT is usually due to ischaemic heart disease. Acutely, amiodarone is the only antiarrhythmic that may be used to treat VT, along with intravenous magnesium, and direct current cardioversion is needed in cardiogenic shock. An implantable cardioverter defibrillator (ICD) may be considered prophylactically. For patients with VT for whom ICD insertion is not contemplated, antiarrhythmic therapy (amiodarone or beta blocker) is a second choice; amiodarone has no evidence for primary prevention after myocardial infarction. Torsades de pointes VT should be distinguished from polymorphic VT with a normal QT interval, the latter treated as standard VT but QT prolonging antiarrhythmics are contraindicated in torsades, which may be caused by metabolic disturbances and drugs. If VT continues, intra-aortic balloon counterpulsation/angiography/VT ablation may be necessary.

What may cause bradycardia?

Causes include acute ischaemia or chronic degeneration of conducting pathways, metabolic disturbances, hypothermia, hypothyroidism, beta blockers, digoxin, verapamil, diltiazam and Lyme disease.

What is meant by the term sudden cardiac death (SCD)?

SCD refers to death from a cardiac cause within 1 hour of symptoms without a known prior condition. Sixty per cent of all cardiac death is SCD, with a male to female ratio of 4 : 1. Causes are listed in Box 2.34.

How might patients be evaluated?

Investigations are largely to exclude coronary heart disease and may include identification of risk factors (hypertension, dyslipidaemia, smoking, diabetes, early family history), echocardiography, nuclear cardiography, coronary angiography, electrophysiological studies, computed tomography, magnetic resonance imaging, positron emission tomography scanning and coronary calcium scoring. In patients clinically affected by a cardiomyopathy

Box 2.34 **Causes of sudden cardiac death (SCD)**

Structural cardiac diseases

- Coronary heart disease (most SCD)
- Cardiomyopathies, e.g. hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Myocarditis
- Congenital heart disease, e.g. mitral valve prolapse, aortic stenosis, tunnelled left anterior descending artery

Ion channelopathies

- Long QT syndrome, an inherited repolarisation disorder causing QT prolongation (QTc > 440 milliseconds) and risk of ventricular arrhythmias (torsade de pointes: 'twisting of points')
- Brugada syndrome, a disorder of abnormal potassium / sodium channelling within the sarcolemma causing right bundle branch block and ST elevation in V1–3 with a risk of polymorphic ventricular tachycardia; three types of Brugada syndrome may occur, with over 100 possible mutations, and the electrocardiographic abnormality may only be evident with exercise in some types, and symptoms sometimes only provoked by bradycardia
- Progressive cardiac conduction disease, a disorder causing variable degrees of heart block
- Catecholaminergic polymorphic ventricular tachycardia, a disorder of cellular calcium handling causing exertional ventricular arrhythmias.

The ion channelopathies and some forms of cardiomyopathy (most HCM, about 25% of DCM, ARVC) are inherited, usually in an autosomal dominant fashion.

'Non-cardiac' causes

- e.g. subarachnoid haemorrhage, aortic rupture, iatrogenic, drug overdose

Gorillas, chimpanzees and other apes appear to be at high risk of HCM and SCD.

the resting electrocardiograph is rarely normal. In gene carriers who seem to be clinically unaffected (incomplete gene expression) it is usually normal. Classically, large-voltage QRS complexes with ST depression and deep T-wave inversion are seen in patients with HCM, although non-specific changes may be seen. In arrhythmogenic right ventricular cardiomyopathy (AVRC), subtle abnormalities may be evident in the right precordial leads (V1–V3) including T-wave inversion, broadening of the QRS and the 'epsilon wave' (notch in the ST segment). Patients with dilated cardiomyopathy (DCM) may also have non-specific abnormalities. Echocardiography or magnetic resonance imaging can help make a definitive diagnosis in HCM and DCM.

What are the indications for an electrophysiological study?

Persistent palpitations, recurrent syncope or pre-syncope with impaired left ventricular function are symptoms suitable for investigation. Radiofrequency ablation (accessory pathways, junctional tachycardias, atrial flutter, AF), and investigation of narrow or broad complex arrhythmias, with or without radiofrequency ablation, are other indications.

Which treatments may be considered for patients at risk of SCD?

Management of patients depends on the cause:

- Treatments for coronary heart disease are by far the biggest intervention overall.
- Cardiac surgery may be indicated, notably coronary artery bypass grafting (CABG) for coronary disease and valve replacement for valvular heart disease. Cardiac surgery carries a higher risk if there is left ventricular dysfunction, hypertension, renal failure or carotid disease. Patients aged over 80 years have a significant immediate risk of death from cardiac surgery (up to 10%), but, for example, a history of blackouts attributable to aortic stenosis may confer an 80% risk of death within the next year and patients with symptomatic valve disease and no significant comorbidity should be referred for consideration of surgery. CABG benefit is harder to prove, except for left main stem disease, three-vessel disease and proximal left anterior descending artery disease (less evidence).
- The risk of SCD from arrhythmias can be reduced by lifestyle changes tailored to removing triggers. For example, participating in competitive sport is universally discouraged. Drugs such as beta blockers and angiotensin-converting enzyme inhibitors are commonly used to reduce the risk of death in patients with DCM, but drugs have not been shown to be useful in reducing the risk of sudden death in patients with HCM or ARVC, although in ARVC symptomatic ventricular arrhythmias may be reduced by sotalol and amiodarone.
- ICDs may be considered (Box 2.35).

What is the role of genetic mutation analysis?

Because genetic testing is less than 100% sensitive, it is recommended only after confirmation of a clinical diagnosis, and even then usually in a limited number of genes that cause disease. Once a definite disease-causing mutation is identified in an affected patient, the main diagnostic role for genetic testing is identification of carriers within a pedigree, a process known as cascade testing. Risk prediction depends mainly on clinical assessment in the case of cardiomyopathy; mutational analysis may determine risk – one specific subgroup of mutations in the gene encoding lamin A/C (LMNA) associated with DCM increases the SCD risk.

What is the value of tracing relatives?

Assuming an autosomal dominant inheritance, all first-degree blood relatives of a proband with cardiomyopathy (the first identified affected member in a family) should undergo cardiogenetic evaluation because they have a 50% chance of being a disease carrier. Case finding can prevent future premature deaths through the timely delivery of

Box 2.35 **Implantable cardioverter defibrillators (ICDs)**

How they work

Since the 1990s transvenous ICD systems have been implanted like a permanent pacemaker. The ICD lead is placed in the right ventricle and has one or two shock coils. It delivers a shock between the coils and the casing of the device. Devices not only defibrillate but also can recognise and treat ventricular tachycardia (VT) by overdrive pacing and have all the functions of a bradycardia pacemaker. Ventricular fibrillation is induced at implantation to ensure function and the device is programmed with several rate zones to respond to a patient's individual arrhythmia rates. Modern devices can incorporate QRS analysis and analyse to minimise the risks of inappropriate shocks in patients with rapidly conducted supraventricular arrhythmias. ICD malfunction includes inappropriate device therapy and failure of therapy.

Evidence

Evidence for ICDs in primary and secondary prevention comes from trials including AVID (survivors of VT or ventricular fibrillation), MADIT (at-risk patients after myocardial infarction with an impaired left ventricular ejection fraction (LVEF) who had not had an arrhythmia incorporating ambulatory electrocardiogram monitoring and electrophysiological testing), MADIT-2 (patients after myocardial infarction with a LVEF $< 30\%$ without electrophysiological testing), DINAMIT (timing after myocardial infarction – at least 1 month after), CABG-PATCH (inherited cardiac conditions) and SCD-HeFt (New York Heart Association class III heart failure due to left ventricular systolic dysfunction).

Indications

- The evidence translates to use of ICDs mostly in the setting of ischaemic cardiomyopathy or heart failure (Case 2.10)
- ICDs are also used in familial cardiac conditions with high risk of sudden cardiac death (e.g. long QT syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome) and are the only intervention shown to reduce sudden cardiac death in most patients with an inherited cardiomyopathy.

Prophylactic use of an ICD in high-risk patients (LVEF $\leq 35\%$ and impaired cardiac autonomic function manifested as depressed heart rate variability or an elevated average heart rate) who have recently had a myocardial infarction does not reduce overall mortality – reduction in arrhythmic death is offset by increased non-arrhythmic death.

treatments that reduce risk. Genotyping of families with long QT syndrome, HCM and Brugada syndrome may allow confirmation of diagnosis and clarification of carrier status, and sometimes guide therapy, e.g. beta blockers and/or ICDs in long QT syndrome.

CASE 2.12 ATRIAL FIBRILLATION

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Dorothy Brooks, aged 78 years

This 78-year-old lady presents with fast palpitations and an irregular pulse. Her current ECG shows atrial fibrillation (AF) but she was in sinus rhythm last year when admitted with chest pain under your team's care. Her current medications are aspirin, atenolol 25 mg, simvastatin 20 mg and ramipril 5 mg, all daily. She experiences intermittent palpitations but is otherwise well. I wonder if she has paroxysmal AF and whether or not she should be considered for anticoagulation.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Dorothy Brooks is a 78-year-old woman who has just been admitted to hospital with fast palpitations. She has had numerous episodes of irregular, fast palpitations over the last year since being admitted to hospital a year ago with a non-ST elevation myocardial infarction. She experiences no ongoing chest pains but does feel moderately breathless if the episodes last for more than an hour or so. Episodes have no diurnal pattern or obvious precipitant. She is usually well, although sometimes has hot flushes during which she feels hot and sweaty. She takes aspirin 75 mg, atenolol 25 mg, simvastatin 20 mg and ramipril 5 mg, daily. Otherwise, she has no significant past medical history of note. She is widowed and lives with her cat. She smoked many years ago and does not drink. She has no particular concerns.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and exploration of symptoms

The history should follow similar lines to that in Case 2.11. In addition, explore the reasons that atrial fibrillation (AF) matters to patients and physicians, namely its causes, symptoms and complications.

Box 2.36 **Symptoms of atrial fibrillation**

- No/minimal symptoms
- Palpitations
- Dyspnoea (exertional or other)
- Fatigue/reduced exercise capacity
- Pre-syncope/syncope
- Symptoms of complications

Box 2.37 **Complications of atrial fibrillation**

- Thromboembolism
- Impaired left ventricular systolic function (heart failure)

■ **Explore symptoms.** Atrial fibrillation may result in any of the symptoms listed in Box 2.36.

These symptoms occur as a result of loss of atrial systole/atrioventricular asynchrony (which reduces left ventricular filling and so cardiac output by up to 50%), variable stroke volume (a slow rate allows a longer filling time and thus improved stroke volume, hence the importance of rate control in AF), the irregular ventricular rate (which patients can be aware of), dyschronotropy (usually fast, and related to activity), mitral regurgitation (ventricular systole may begin when the mitral valve is still open) or the underlying cause.

■ **Consider potential complications.** AF means atrial 'quivering' or disordered contraction and this predisposes to two important complications (Box 2.37).

Total mortality is doubled, largely because of stroke, which is increased six-fold and up to 18-fold for those with rheumatic heart disease. Stasis leads to thrombus formation, especially in the left atrial appendage, and thrombi are often large, provoking devastating strokes. Morbidity relates to age and underlying cause, and annual stroke risk is 1.5% for patients aged 50–59 rising to 23.5% in patients aged 80–89.

Patient perspective

She has no particular concerns.

Past medical history

AF alerts physicians to underlying disease. The leading causes are listed in Box 2.38.

Drug and allergy history

She is taking a range of secondary prophylaxis, but at suboptimal doses.

Family history

Relevance here is unlikely.

Social history

There are no obvious worries, but she lives alone and should be asked if things are all well at home.

Box 2.38 **Causes of atrial fibrillation (AF)**

The big five causes are:

1. Coronary artery disease
2. Hypertension
3. Valvular heart disease
4. Thyroid dysfunction
5. Alcohol.

Other conditions associated with AF include:

- Ageing (possibly through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances)
- Symptomatic heart failure including tachycardiomyopathy
- Cardiomyopathies, including primary electrical cardiac diseases (really any structural or electrical heart defect, e.g. sinus node disease due to fibrosis, Wolff–Parkinson–White syndrome, myocarditis)
- Atrial septal defect and other congenital heart defects
- Obesity
- Diabetes mellitus
- Chronic obstructive pulmonary disease, any chronic respiratory disease, pulmonary embolus
- Infection
- High-caffeine supplements.

Where absolutely no cause can be identified, the condition has traditionally been termed 'lone AF', a term usually reserved for patients < 60 years of age.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ If atrial fibrillation (AF) is confirmed, an initial decision to rate control is probably best as it cannot be unequivocally established that this episode came on within the last 48 hours; further, she has probably had numerous previous episodes and asymptomatic paroxysmal AF is common. Digoxin loading at 500 μg followed by 500 μg 6 hours later and then 125 μg daily is appropriate, as would be increasing the dosage of beta blockade (safer to use a short-acting agent such as metoprolol in acute settings).
- ◆ A troponin assay as well as routine haematobiochemistry, including potassium, magnesium and calcium levels, and thyroid function tests should be obtained, although troponin levels are sometimes elevated by AF alone.
- ◆ Low-molecular-weight heparin at a therapeutic dose for thromboembolic prophylaxis should be commenced, and warfarin subsequently considered.
- ◆ She should have an echocardiogram in the near future.
- ◆ Her simvastatin should be increased to 40 mg and her ramipril to 10 mg if there are no contraindications.

Discussion

How common is AF?

AF is the most common sustained cardiac arrhythmia, occurring in 1–2% of the population. The prevalence increases with age, from 0.5% at 40–50 years to 5–15% at 80 years. Men are more often affected than women.

Why is AF important?

- Death rates are independently doubled by AF. Only antithrombotic therapy has been shown to reduce AF-related deaths.
- AF confers a five-fold increased risk of stroke. Stroke in AF is often severe and results in long-term disability or death, and in survivors is more likely to recur. Approximately every fifth stroke is due to AF; furthermore, undiagnosed 'silent AF' is a likely cause of some 'cryptogenic' strokes. Paroxysmal AF carries the same stroke risk as permanent or persistent AF. Cognitive dysfunction, including vascular dementia, may be related to AF.
- Hospitalisations due to AF account for one-third of all admissions for cardiac arrhythmias. Acute coronary syndrome (ACS), aggravation of heart failure, thromboembolic complications and acute arrhythmia management are the main causes.
- Quality of life and exercise capacity are impaired in patients with AF.
- Left ventricular function is often impaired by the irregular, fast ventricular rate and by loss of atrial contractile function and increased end-diastolic left ventricular filling pressure.

What is the pathophysiology of AF?

How AF is sustained

The electrical properties of the atria are altered by sustained AF, making the atria more susceptible to initiation and maintenance of AF. Sustained AF then induces further electrophysiological and structural alterations known as atrial remodelling:

- Tachycardia causes calcium overload in atrial myocytes; this alters gene expression leading to downregulation of one type of calcium current, a shortening of the refractory period and a decrease in wavelength, promoting multiple wave re-entry (electrical remodelling).
- Increased cell volume, sarcomere misalignment, proteolysis, loss of contractile elements and accumulation of glycogen lead to atrial myopathy (structural remodelling).

These factors explain why AF may recur early after electrical cardioversion, why paroxysmal AF may progress to chronic AF and why chronic AF is harder to treat.

Sequelae

All of these factors lead to an increasing tendency for irregular, often fast atrial activity, and thromboembolic risk due to stasis of blood flow and endothelial dysfunction.

Atrial factors

Any structural heart disease may trigger progressive structural remodelling in both the ventricles and the atria. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis occur. Electrical remodelling contributes to the increasing stability of AF during the first days after its onset. The main cellular mechanisms underlying the shortening of the refractory period are downregulation of the L-type calcium inward current and upregulation of inward rectifier potassium currents.

Electrophysiological mechanisms

The initiation and perpetuation of a tachyarrhythmia requires triggers for its onset and a substrate for its maintenance. Various mechanisms are likely to coexist. *Focal mechanisms* might involve both triggered activity and re-entry. Single rapid macrore-entry circuits produce wavefronts emanating from a primary driver (rotor, which may be fixed or moving) which break against regions of varying refractoriness; this gives rise to the irregular global activity that characterises the arrhythmia, a bit like a large mother wave breaking against rocks of all different shapes and sizes, producing all sorts of smaller, diversely directed waves. The single focus also fires at an automatic, regular but very rapid rate that cannot be followed by the rest of the atrial tissue in a 1 : 1 fashion, so producing fibrillatory conduction. Because of shorter refractory periods as well as abrupt changes in myocyte fibre orientation, the pulmonary veins have a stronger potential to initiate and perpetuate atrial tachyarrhythmias. Arrhythmogenic foci in the pulmonary veins may be amenable to ablation, but access is difficult and through puncture of the atrial septum. In the *multiple wavelet hypothesis,* AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. A combination of single and multiple foci may be at play.

Genetic predisposition

AF has a familial component, especially AF of early onset. Numerous inherited cardiac syndromes associated with AF include short and long QT syndromes and Brugada syndrome.

How is AF defined?

AF is defined as a cardiac arrhythmia with the following characteristics:

- The electrocardiogram shows 'absolutely' irregular RR intervals
- There are no distinct P waves on the electrocardiogram
- The atrial cycle length (when visible) is usually variable.

What types of AF are there?

Clinically, there are five types of AF (Table 2.23).

What are the acute management priorities in AF?

The acute management of AF focuses on relief of symptoms and assessment of AF-associated risks and should include the following.

Table 2.23 Types of atrial fibrillation (AF)

First diagnosed AF	Every patient presenting for the first time
Paroxsymal	Duration < 7 days (usually < 48 hours) Terminates spontaneously
Persistent	Duration > 7 days Indefinite without cardioversion
Long-standing persistent AF	Duration > 1 year
Permanent	Duration > 7 days Sinus rhythm not possible

Table 2.24 Cardiac failure, hypertension, age, diabetes, stroke (doubled) ($CHADS_2$) score

	Condition	Points
C	Congestive heart failure	1
H	Hypertension: above 140 / 90 mmHg (or treated on medication)	1
A	Age ≥ 75 years	1
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischaemic attack	2

Table 2.25 CHA_2DS_2–VASc score

	Condition	Points
C	Congestive heart failure or moderate to severe left ventricular dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75 years ('major' risk factor)	2
D	Diabetes mellitus	1
S_2	Stroke / transient ischaemic attack / thromboembolism ('major' risk factor)	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

Determination of symptoms

Determination of the European Heart Rhythm Association (EHRA) score is useful: I 'No symptoms'; II 'Mild symptoms' – normal daily activity not affected; III 'Severe symptoms' – normal daily activity affected; IV – 'Disabling symptoms' – normal daily activity discontinued.

Estimation of stroke risk and consideration of other complications

Most patients with acute AF will require anticoagulation unless they are at low risk of thromboembolic complications (no stroke risk factors) and no cardioversion is necessary (e.g. AF terminates within 24–48 hours).

Search for causes

Underlying causes should be sought. An echocardiogram is useful to detect ventricular, valvular and atrial disease. Thyroid function tests should be included in the initial blood screen. Patients with persistent signs of left ventricular dysfunction and/or signs of myocardial ischaemia are candidates for coronary angiography.

What do you know about antithrombotic therapy in AF?

Risk stratification is a precursor to treatment decisions.

Risk stratification for stroke and thromboembolism

Various stroke risk schemes have (artificially) categorised stroke risk into 'high', 'moderate' and 'low' risk strata, but as these have low predictive value there is now increased emphasis on the presence of stroke risk factors. The simplest risk assessment scheme is the $CHADS_2$ score (cardiac failure, hypertension, age, diabetes, stroke (doubled)) (Table 2.24).

The CHA_2DS_2-VASc score refines and extends the $CHADS_2$ score by including additional common stroke risk factors (Table 2.25). The $CHADS_2$ score does not include many stroke risk factors such as some types of valvular heart disease (mitral stenosis or prosthetic heart valves), which would categorise such 'valvular' AF patients as 'high risk'. Risk factors are cumulative and the presence of one 'major' risk factor (stated in Table 2.24) or the simultaneous presence of two or more 'clinically relevant non-major' risk factors (those others in Table 2.25) would justify a stroke risk that is high enough to require anticoagulation.

Antithrombotic therapy

Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thromboembolism, rather than on an artificial division into high-, moderate- or low-risk categories (Box 2.39).

Evidence for antithrombotic agents

Numerous clinical trials have provided an extensive evidence base for antithrombotic therapy in AF:

- Anticoagulation with a vitamin K antagonist (VKA) (versus control) for patients with AF with ≥ 1 stroke risk factor produces a 64% risk reduction provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient's values and preferences.

Box 2.39 **Antithrombotic therapy in atrial fibrillation based on risk stratification**

- Those with no risk factors are truly low risk and can be managed without antithrombotic therapy.
- The $CHADS_2$ score should be used as a simple initial means of assessing stroke risk. In patients with a $CHADS_2$ score ≥ 2, oral anticoagulation (OAC) therapy with a vitamin K antagonist (VKA) is recommended to achieve an international normalised ratio target of 2.5.
- In patients with a $CHADS_2$ score of 0–1, or where a more detailed stroke risk assessment is indicated, a more comprehensive risk factor-based approach is recommended incorporating other risk factors for thromboembolism such as the CHA_2DS_2-VASc score. In patients with a CHA_2DS_2-VASc score of ≥ 2 (one major risk factor or ≥ 2 clinically relevant non-major risk factors) OAC is recommended. In patients with a CHA_2DS_2-VASc score of 1, either OAC or aspirin 75–325 mg daily may be considered.

Newer OAC drugs, such as dabigatran etexilate, may be considered and may confer lower risk of intracranial bleeding.

- Data from all comparisons of antiplatelet agents and control groups show 22% risk reduction. Pharmacologically, near-complete platelet inhibition is achieved with aspirin 75 mg, and low-dose aspirin is safer than higher doses.
- Direct comparison between a VKA and aspirin demonstrates that a VKA is significantly superior. In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events –Warfarin arm (ACTIVE W) trial, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin. The Aspirin arm (ACTIVE A) trial found that major vascular events were reduced in patients receiving aspirin–clopidogrel, compared with aspirin monotherapy, but major bleeding was significantly increased and broadly similar to that seen with VKA therapy.
- Several new anticoagulant drugs – broadly two classes, oral direct thrombin inhibitors (e.g. dabigatran etexilate and AZD0837) and oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban, betrixaban, YM150) – are being developed for stroke prevention in AF. Dabigatran may be used to prevent stroke and systemic embolism in people with non-valvular AF with at least one of the following risk factors: previous stroke or transient ischaemic attack (TIA) or systemic embolism; left ventricular ejection fraction ≤ 40%; symptomatic heart failure; age ≥ 75 years; age ≥ 65 years with one of diabetes, coronary artery disease or hypertension.

Risk of bleeding

Table 2.26 HAS-BLED score

Clinical characteristic	Points
Hypertension (systolic blood pressure ≥ 160 mmHg)	1
Abnormal live function	1
Abnormal renal function	1
Age ≥ 65 years	1
Stroke in past	1
Bleeding	1
Labile INRs	1
Taking other drugs	1
Alcohol intake at the same time	1

An assessment of bleeding risk should be made before starting anticoagulation. Despite anticoagulation of more elderly patients with AF, rates of intracerebral haemorrhage are considerably lower than in the past, typically between 0.1% and 0.6%, which may reflect lower anticoagulation intensity, more careful dose regulation or better control of hypertension. Intracranial bleeding increases with international normalised ratio (INR) values 3.5–4.0, and there is no increment in bleeding risk with INR values between 2.0 and 3.0 compared with lower INR levels. Various bleeding risk scores have been validated for bleeding risk in anticoagulated patients. A HAS-BLED score (Table 2.26) of ≥ 3 indicates 'high risk', and some caution and regular review is needed following initiation of antithrombotic therapy, whether with VKA or aspirin.

Optimal INR

The level of anticoagulation is expressed as the INR, derived from the ratio between the actual prothrombin time and that of a standardised control serum. Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF. Whilst a lower target INR range (1.8–2.5) has been proposed for the elderly, this is not based on evidence and studies suggest a two-fold increase in stroke risk at an INR of 1.5–2.0. The maintenance, safety and effectiveness of the INR within range can be influenced by the pharmacogenetics of VKA therapy, particularly the cytochrome P450 2C9 gene (*CYP2C9*) and the vitamin K epoxide reductase complex 1 gene (*VKORC1*).

AF in special situations

Paroxysmal AF

Stroke risk in paroxysmal AF is not different from that in persistent or permanent AF and thus patients with paroxysmal AF should receive oral anticoagulation (OAC) according to their risk score.

Perioperative anticoagulation

Patients with AF who are anticoagulated require temporary interruption of VKA treatment before surgery or an invasive procedure. The risk of clinically significant bleeding should be weighed against the risk of stroke and thromboembolism. If the VKA is warfarin, which has a half-life of 36–42 hours, treatment should be interrupted 5 days before surgery. In patients with a mechanical heart valve or AF at high risk for thromboembolism, 'bridging' anticoagulation with therapeutic doses of either low-molecular-weight heparin or unfractionated heparin should be considered.

Stable vascular disease

Many anticoagulated AF patients have stable coronary or carotid artery disease and/or vascular disease, and common practice is to treat such patients with a VKA plus one antiplatelet drug, usually aspirin. This does not reduce the risk of stroke or vascular events (including myocardial infarction), but substantially increases bleeding events.

Acute coronary syndrome and/or percutaneous coronary intervention (PCI)

Guidelines for ACS and/or PCI recommend combination antiplatelet therapy (aspirin and clopidogrel) after an ACS, and a stent (4 weeks for a bare-metal stent, 6–12 months for a drug-eluting stent). VKA non-treatment is associated with an increase in mortality and major adverse cardiac events, with no significant difference in bleeding rates. Thus triple therapy seems to have an acceptable risk–benefit ratio provided it is kept short (e.g. 4 weeks) and the bleeding risk is low. Consensus is that drug-eluting stents should be avoided and triple therapy (VKA, aspirin and clopidogrel) used in the short term, followed by longer therapy with VKA plus a single antiplatelet drug (either clopidogrel or aspirin). In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding year),VKA monotherapy should be used.

Elective PCI

Triple therapy (VKA, aspirin, and clopidogrel) should be administered for a minimum of 1 month after implantation of a bare-metal stent, but for much longer with a drug-eluting stent.

Acute stroke

There are limited trial data to guide management, and there is concern that patients within the first 2 weeks after cardioembolic stroke are at greatest risk of recurrent stroke because of further thromboembolism. However, anticoagulation in the acute phase may result in intracranial haemorrhage or haemorrhagic transformation of the infarct. In patients with AF and an acute TIA, OAC therapy should be considered as soon as possible in the absence of infarction or haemorrhage. In patients with AF presenting with an acute stroke or TIA, uncontrolled hypertension should be appropriately managed before antithrombotic treatment is started, and cerebral imaging performed to exclude haemorrhage. In the absence of haemorrhage, anticoagulation should begin after 2 weeks, but in the presence of haemorrhage anticoagulation should not be given.

Cardioversion

Increased risk of thromboembolism following cardioversion is well recognised. Therefore anticoagulation is considered mandatory before elective cardioversion for AF of > 48 hours or AF of unknown duration. VKA treatment (INR 2.0–3.0) should be given for at least 3 weeks.

Atrial flutter

The risk of stroke linked to atrial flutter is similar to that seen in AF. Thus, thromboprophylaxis in patients with atrial flutter should follow the same guidelines as in AF patients.

What do you know about acute rate and rhythm management in AF?

The acute management of patients with AF is driven by acute protection against thromboembolic events and acute improvement of cardiac function. The severity of AF-related symptoms should drive the decision for acute restoration of sinus rhythm (in severely compromised patients) or acute management of the ventricular rate (in most other patients).

Acute rate control

In stable patients this can be achieved by oral beta blockers or non-dihydropyridine calcium channel antagonists. In severely compromised patients, intravenous verapamil or metoprolol can be used. Either oral or intravenous digoxin or intravenous amiodarone is preferable in patients with concomitant heart failure or hypotension. If the ventricular rate is very fast (200–300) or delta waves are seen, a rapidly conducting accessory (pre-excitation) pathway is likely and intravenous flecainide and/or direct current cardioversion (DCCV) is recommended; atrioventricular node blockers (e.g. adenosine, digoxin, verapamil, diltiazem) are contraindicated in this situation as they potentially further accelerate the ventricular response.

Pharmacological cardioversion

Many episodes of AF terminate spontaneously within the first hours or days. If medically indicated (e.g. compromised patients, patients who remain symptomatic despite adequate rate control), a bolus administration of an antiarrhythmic drug may be considered. The conversion rate is lower than with electrical cardioversion, but does not require sedation or anaesthesia. Class I or class III antiarrhythmics are commonly used for cardioversion and maintenance of sinus rhythm. Flecainide, propafenone and amiodarone may be effective in descending order, but class Ic drugs (flecainide and propafenone) should be avoided in ischaemic heart disease and impaired left ventricular function. Class Ic antiarrhythmics are also dangerous in atrial flutter. Flutter has an average atrial rate of 300 and with 2 : 1 block an average ventricular rate of 150. Class Ic antiarrhythmics may slow the atrial rate to, for example, 200, which can then be conducted via an intact atrioventricular node to produce a similar ventricular rate.

Ibutilide and vernakalant may also be used, with their own contraindications. Ibutilide and sotalol are more effective for conversion of atrial flutter. Repeat oral pharmacological cardioversion ('pill-in-the-pocket' therapy) may be appropriate for selected ambulatory patients once the safety of such an intervention has been established.

Direct current cardioversion (DCCV)

DCCV is an effective method of converting AF to sinus rhythm. Unless adequate anticoagulation has been documented for 3 weeks or AF is < 48 hours from a definite onset, transoesophageal echocardiography should be performed to rule out atrial thrombi. Complications include thromboembolic events and arrhythmias. Recurrences of AF may be immediate within minutes, early during the first 5 days or late. Factors that predispose to AF recurrence include:

- Duration of AF (especially more than 3 months)
- Heart failure / structural heart disease
- Hypertension
- Age
- Left atrial diameter > 6.5 cm.

When might you consider long-term rate control in AF and what might you use?

Rate control is the only approach for permanent AF but has gained popularity for persistent AF. Numerous randomised controlled trials, including the AFFIRM study, have demonstrated no difference in the endpoints of mortality or disabling stroke between rate versus rhythm control, with more side effects from drug treatment in the rhythm control groups. Furthermore, sinus rhythm is often not maintained and rhythm control does not lower the need for antithrombotic therapy. Rate control may now be considered for patients aged > 65 years; Table 2.27 lists factors that can aid decision making about rhythm versus rate control. It is important to understand, however, that younger patients, especially those with symptoms or heart failure, benefit more from rhythm control.

Infrequent, well-tolerated paroxysmal AF may require no treatment. Beta blockers and digoxin are otherwise first-line choices. Digoxin is ineffective in paroxysmal AF, exercise and states with a high sympathetic drive such as thyrotoxicosis and critical illness; and is potentially dangerous if there is underlying Wolff–Parkinson–White syndrome. In patients with good left ventricular function, beta blockers or non-dihydropyridine calcium channel blockers (verapamil and diltiazam) are the drugs of choice if there are no contraindications. Beta blockers with digoxin have the potential in elderly people to augment long sinus pauses, and beta blockers with rate-limiting calcium channel blockers are highly dangerous because of the risks of heart block and / or suppression of contractility and should not be prescribed. In heart failure, digoxin or amiodarone should be used. Dronedarone is effective as a rate-controlling drug for chronic treatment, significantly decreasing the heart rate at rest and during exercise. The effects of dronedarone are additive to those of other rate control agents, but it is not currently approved for permanent AF. Other class I antiarrhythmic drugs are not effective for rate control. Sotalol should not be used solely for rate control.

Table 2.27 Rhythm or rate control first

Try rhythm control first	Try rate control first
Symptomatic	Age over 65 years
Younger	Coronary artery disease
First presentation of lone atrial fibrillation	Contraindications to antiarrhythmic drugs
Secondary to a treated or corrected precipitant	Unsuitable for cardioversion
Heart failure	

How might long-term rhythm control be achieved?

- Standard beta blockers are now recommended as first-line treatment in all patients (structural or non-structural heart disease) without contraindications, to maintain sinus rhythm. Sotalol is not effective for cardioversion, but has some efficacy in maintaining sinus rhythm in patients with structural heart disease, including ischaemic heart disease.
- Class Ic drugs (flecainide or propafenone) are better tolerated and more effective than class Ia drugs (quinidine and disopyramide), but contraindicated in structural heart disease including ischaemic heart disease and left ventricular dysfunction.
- Amiodarone may be more effective than sotalol and class I drugs, but is limited in the long term by side effects (skin rash, thyroid function disturbance, pulmonary fibrosis, corneal deposits).
- There is increasing interest in novel antiarrhythmics acting on ion channels involved in atrial repolarisation (atrial repolarisation delaying agents) and in non-traditional antiarrhythmics which may have antiarrhythmic properties such as angiotensin-blocking agents and statins.

Thus a summary of drug choices according to comorbidity is:

- Beta blockers, sotalol, flecainide, propafenone, amiodarone or dronedarone are suitable for AF with no or minimal heart disease or AF associated with hypertension without significant left ventricular hypertrophy.
- Sotalol or amiodarone or dronedarone are suitable for AF associated with coronary artery disease.
- Amiodarone or dronedarone are suitable for AF associated with hypertension and left ventricular hypertrophy or for AF associated with stable New York Heart Association class I / II heart failure, and amiodarone for more severe heart failure.

What non-pharmacological therapies are you aware of for AF?

These include radiofrequency catheter ablation of the atrioventricular node and permanent pacing ('ablate and pace', best reserved as a last resort), obliteration of the left atrial appendage and implantable atrial defibrillators. Catheter ablation is recommended after failure of at least one antiarrhythmic drug or where antiarrhythmic drugs are contraindicated or not suitable. Pulmonary vein isolation to prevent induction of AF (by rapid repetitive pulmonary vein ectopic activity emanating from 'sleeves' of the atrial myocardium inside the pulmonary veins) has a high success rate.

How might you manage atrial flutter?

Recommendations for atrial flutter are similar to those for AF. Carotid sinus massage or adenosine may transiently slow atrioventricular conduction, making the flutter waves more obvious. Atrial flutter ablation, a definitive cure, should be considered at an early stage for recurrent atrial flutter.

CASE 2.13 DYSLIPIDAEMIA

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Jean Buchanan, aged 64 years
> Thank you for advising on the treatment of this lady's lipid profile. She has type 2 diabetes and her total cholesterol 6 months ago was 7.5 mmol/l. She is now on the maximum dose of atorvastatin, and her cholesterol has fallen to 6.0 mmol/l with a high-density lipoprotein of 0.9 mmol/l and raised triglycerides. She is overweight. She also takes metformin, twice daily insulin, perindopril, bendroflumethiazide and aspirin. She has a slightly raised thyroid-stimulating hormone but a normal thyroxine, which I am monitoring.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Jean Buchanan is a 64-year-old woman with raised cholesterol, 7.5 mmol/l, discovered at her diabetes check at the surgery 6 months ago. Her atorvastatin was increased to a higher dose of 80 mg and when rechecked recently her cholesterol was 6.0 mmol/l. She feels well in herself and is fully independent. She was diagnosed with diabetes 10 years ago and since then has developed numerous complications – she has had laser therapy for diabetic retinopathy and had to give up work as a secretary because of eye disease. She has proteinuria, recently discovered. She has numbness of both feet and a small diabetic foot ulcer. She has hypertension, treated with perindopril 4 mg once a day and bendroflumethiazide 2.5 mg once a day. She also takes aspirin 75 mg once a day, metformin 1 g t.d.s. and twice-daily insulin. She is overweight, despite advice from the practice on diet and exercise, and eats three meals a day: breakfast of cereal and buttered toast, lunch of soup with bread and butter and dinner of meat, potatoes and vegetables. She snacks between meals, especially if she increases her insulin dose. Home blood glucose monitoring reveals levels of 9–14. Her glycated haemoglobin (HbA$_{1c}$) is 10 mmol/l. She does not smoke or drink alcohol. She is very concerned about her cholesterol level, as she been told it is a risk factor for ischaemic heart disease and both her parents died of heart attacks.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Take a full history of her:

- Dyslipidaemia (many patients know their exact levels)
- Diabetes, including complications (retinopathy, nephropathy, neuropathy)
- Cardiovascular disease (CVD) risk (age and sex, level of diabetes control, hypertension, smoking status, family history, excess weight, alcohol intake, lack of exercise).

She very probably has dyslipidaemia secondary to diabetes, but it is important to be aware of the types of dyslipidaemia (Table 2.28) and consider other potential contributors. The World Health Organization numerical classification is largely superseded in practice by a descriptive one. Hypercholesterolaemia usually results from nutritional factors such as a diet high in saturated fats combined with an underlying polygenic predisposition; monogenic causes are rare. Hypercholesterolaemia may have an entirely genetic cause, as in monogenic familial hypercholesterolaemia (Table 2.28) in which low-density lipoprotein (LDL) is raised from birth.

Table 2.28 Classification of dyslipidaemia

	Prevalence	Cause / pathophysiology	Biochemical features	Clinical features
Common or polygenic hypercholesterolaemia	70% The common hypercholesterolaemia, representing the right side of the normal distribution curve and affecting 20–80% of the population, depending upon cut-off point	High saturated fat intake and polygenic predisposition	Excess VLDL, converted quickly to LDL so that VLDL and triglyceride levels normal but LDL raised	Increased CVD risk Occasionally corneal arcus, xanthelasmata
Heterozygous familial hypercholesterolaemia	0.2% (1 in 500) Much rarer homozygotes (around 1 in 10^6) develop childhood CVD	Autosomal dominant monogenic Mutation in LDL receptor prevents binding or internalising of LDL Very rarely abnormal apo B100	*Diagnostic criteria from the Simon Broome FH register:* *Definite diagnostic criteria:* TC > 7.5 mmol / l in adults over 16 years or LDL > 4.9 mmol / l *plus* Either tendon xanthomata in person or first- or second-degree relative and / or DNA evidence of LDL receptor mutation or defective apo B100 or a PCSK9 mutation *Possible diagnostic criteria:* TC > 7.5 mmol / l in adults over 16 years or LDL > 4.9 mmol / l *plus one of* Family history of myocardial infarction < 50 years in second-degree relative or < 60 in first-degree relative Family history of raised TC > 7.5 mmol / l in first- or second-degree relative	Tendon xanthomata almost pathognomonic, commonly over Achilles, knuckles, tibial tuberosity at patellar insertion, elbows; overlying skin normal colour Occasionally corneal arcus, xanthelasmata Cholesterol raised from childhood and CVD events typically in men 30–50 years with a > 50% risk of premature CHD by age 50 and women 50–70 years with a > 30% risk by age 60, with mortality at least 10 times expected
(Familial) combined hyperlipidaemia	10% More common than FH Considerable overlap with secondary causes, especially diabetes and the metabolic syndrome	Many abnormalities, e.g. variations in LPL or its activators / inhibitors apo CII / CIII or CETP	Raised TC, triglycerides (2–10 mmol / l), LDL, VLDL Low HDL, partly because of impaired LPL activity – LPL, in catabolising triglycerides from lipoproteins, generates HDL	High CVD risk Occasionally corneal arcus, xanthelasmata
Small dense LDL and hyperapobetalipoproteinaemia / familial defective apo B	0.2%	Monogenic	Standard laboratory LDL levels are normal Small, dense LDL particles in excess (could be detected by the presence of apo B)	Even more susceptible than LDL to oxidisation and highly atherogenic High CVD risk

Table 2.28 Classification of dyslipidaemia—cont'd

	Prevalence	Cause / pathophysiology	Biochemical features	Clinical features
Type III hyperlipoproteinaemia (dysbetalipoproteinaemia or remnant removal disease)	0.02% Rare	Monogenic Usually apo E2 homozygosity, normally important for chylomicron remnant and VLDL remnant removal	Mixed TC (7–12 mmol / l) and triglyceride (5–20 mmol / l) lipidaemia	Striate palmar and tuberoeruptive xanthomata High CVD risk
Moderate and severe (> 10 mmol / l) hypertriglyceridaemia	Many formerly considered to have isolated hypertriglyceridaemia now classified as combined as acceptable cholesterol thresholds have lowered Prevalence of severe probably around 0.1% or 1 in 1000	Familial LPL deficiency or heterozygous LPL mutation Sometimes associated secondary factor, e.g. obesity, alcohol, diabetes, hypothyroidism (all cause hypertriglyceridaemia)	Fasting triglycerides > 10 mmol/l Raised chylomicrons and VLDL (both compete for the same clearance mechanism, LPL) Chylomicronaemia can produce spectacularly raised triglycerides e.g. > 100 mmol / l TC can be markedly elevated with normal LDL because chylomicrons and VLDL contain it	Eruptive xanthomata – yellow nodules extensor surfaces (elbows, knees, buttocks, back) in hypertriglyceridaemia Hepatosplenomegaly rarely Acute pancreatitis with triglyceride > 20–30 mmol / l Milky plasma Pseudohyponatraemia
Secondary hyperlipidaemia	Common	Hypothyroidism Cholestasis Nephrotic syndrome Cushing's syndrome Anorexia Drugs, e.g. thiazides, ciclosporin Diabetes Metabolic syndrome Alcohol Monoclonal gammopathy Dialysis Drugs, e.g. glucocorticoids, beta blockers	High LDL High triglycerides and low HDL	High CVD risk

apo, apolipoprotein; CETP, cholesterylester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; TC, total cholesterol; VLDL, very-low-density lipoprotein cholesterol.

Patient perspective

Acknowledge and explore her concerns about ischaemic heart disease.

Past medical history

Explore all the usual CVD suspects, including her diabetes complications.

Drug and allergy history

Review her lipid-lowering, blood pressure and diabetes drugs.

Family history

Ask about the ages of family members when they suffered CVD events.

Social history

Explore her reasons for giving up work and the impact of this.

Discussion

Why is cholesterol important?

Cholesterol is essential for cell membrane structure and a precursor for steroid hormone and bile acids.

SUMMARY BOX – ASSESSMENT AND PLAN

- Unfortunately, she is already taking a good range of evidence-based primary prophylaxis.
- Her diet should be reviewed, and there may be an indication for considering a second lipid-lowering agent.
- Her overall cardiovascular disease (CVD) risk management is more important than focusing only on her cholesterol level.
- Tighter control of her diabetes is imperative in reducing her overall CVD risk, including its benefits on her lipid profile; she might be considered for a long-acting insulin analogue such as glargine and short-acting analogues.

What are lipoproteins?

Lipoproteins are complexes of lipid and protein that carry hydrophobic plasma lipids, notably cholesterol and triglycerides. Abundance of larger, triglyceride-containing lipoproteins can turn plasma milky. Cholesterol and triglycerides form the core of lipoproteins and phospholipids and apolipoproteins form the surface; the latter are synthesised largely in the liver and are pivotal in lipid transport and metabolism. Lipoproteins are classified, through escalating density, as chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

What types of apolipoprotein are there?

Apo B100 is the major apolipoprotein of VLDL and LDL. It is the ligand for the removal of LDL by the LDL receptor, a cell surface molecule that binds and internalises lipoproteins containing apo B100 or apo E. Apo B48 is the major apolipoprotein of chylomicrons. Apo Cs are present in all plasma lipoproteins (traces in LDL) and tend to inhibit the removal of plasma chylomicrons and VLDL remnants by the liver. Apo CII activates lipoprotein lipase (LPL). LPL hydrolyses triglycerides in chylomicrons and VLDL. Deficiency causes severe hypertriglyceridaemia. Apo CIII inhibits LPL activity. Apo E is found in chylomicrons, VLDL and HDL and is a ligand for their uptake by both the LDL receptor and LDL-receptor-related protein (LRP). There are three major alleles, E2, 3 and 4; E2 binds most easily to the LDL receptor. Apolipoproteins AI, AII and AIV are found mostly on HDL. Apo AI is integral to HDL and its deficiency causes HDL deficiency. It also activates lecithin–cholesterol acetyltransferase (LCAT).

What happens to dietary (exogenous) lipids? (Fig. 2.6A)

Dietary triglycerides and cholesterol are incorporated into chylomicrons in gut mucosa. Chylomicrons are fat droplets with a very high triglyceride concentration, and the means by which cholesterol is transported from the gut to the liver. They enter the circulation via the thoracic duct, where HDL donates apo CII molecules, activating hydrolysis of triglycerides by LPL to free fatty acids (FFAs) and glycerol on capillary endothelial cells in fat and muscle. FFAs are used for energy in adjacent tissue or stored as fat. Insulin helps stimulate LPL and so diabetes impairs triglyceride clearance, as can LPL deficiency. Most circulating LPL is associated with LDL. Apo E allows chylomicron remnants (after the triglyceride core has been hydrolysed and apo CII has recirculated back to HDL) to bind to hepatic LDL receptors (or similar lipoprotein receptor proteins referred to as LRP). The overall results are utilisation or storage of triglycerides and uptake of cholesterol by the liver. Cholesterol can also be synthesised *de novo* in the liver by the action of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, and to a lesser extent cholesterol can be synthesised *de novo* in the gut or central nervous system. Liver cholesterol can be used for bile acid formation through the action of 7α-hydroxylase, excreted as cholesterol in bile, incorporated into membranes or resecreted into the circulation either directly as VLDL or by conversion to triglyceride by the action of acyl-CoA:cholesterol acyltransferase and microsomal triglyceride transfer protein.

What is endogenous lipid transport and metabolism?

This refers to the transfer of lipids from the liver to the peripheral tissues and back.

How is lipid transported from the liver to peripheral tissues? (Fig. 2.6B)

This is via the apo B100 system, and concerns VLDL, IDL and LDL. In the liver, cholesterol is taken up from chylomicron remnants or synthesised *de novo* and triglycerides are made from FFAs taken up from plasma or synthesised *de novo*. These core lipids are packaged with apo B100 and phospholipid into VLDL and secreted into plasma where apolipoproteins C and E are added. VLDL is triglyceride rich, even more so in states of triglyceride excess such as overeating, diabetes and alcohol consumption. In the plasma, LPL hydrolyses VLDL triglycerides to create smaller, denser VLDL remnants (also known as IDL). VLDL remnants (IDL) are still relatively triglyceride rich (more so than LDL and less so than VLDL), but progressively lose triglyceride as more and more triglyceride is hydrolysed by LPL. VLDL remnants can re-enter the liver via apo E binding to the LDL receptor or, after stepwise LPL activity, become LDL, apo B100 being the only remaining surface protein on LDL. LDL is the means by which cholesterol is delivered to most tissues. Some LDL is taken up by the liver via the LDL receptor. Some is delivered to tissues such as adrenals and gonads and used for steroid hormone synthesis.

What influences LDL levels as well as diet?

LDL levels are influenced by LDL receptor availability or activity; they are downregulated when liver cholesterol is replete.

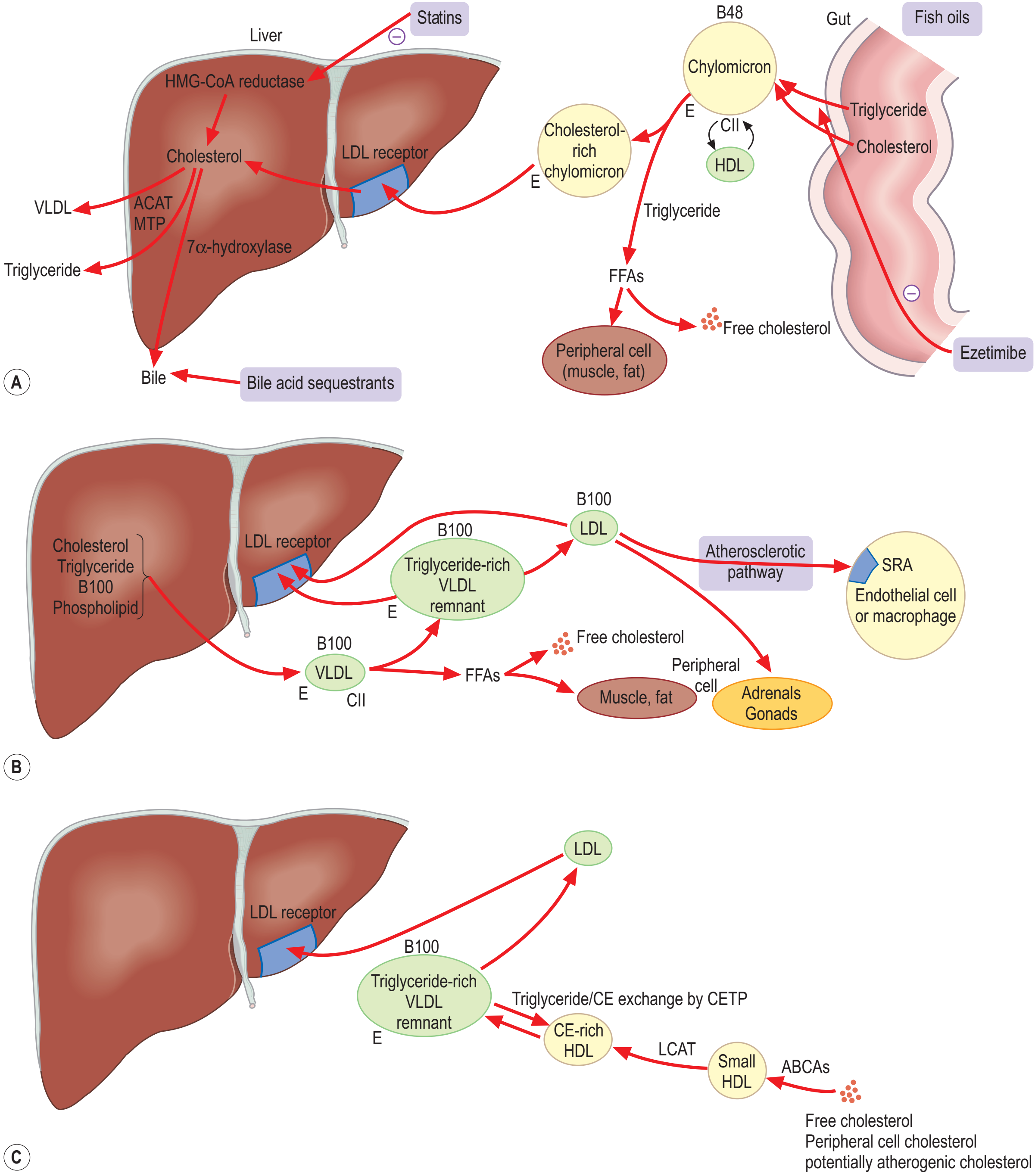

Statins
Liver
HMG-CoA reductase
Cholesterol
LDL receptor
VLDL
ACAT
MTP
7α-hydroxylase
Triglyceride
Bile
Bile acid sequestrants
A
B48
Chylomicron
Gut
Fish oils
Cholesterol-rich chylomicron
E
CII
HDL
Triglyceride
Cholesterol
Triglyceride
FFAs
Free cholesterol
Peripheral cell (muscle, fat)
Ezetimibe
Cholesterol
Triglyceride
B100
Phospholipid
LDL receptor
B100
LDL
B100
Triglyceride-rich VLDL remnant
E
Atherosclerotic pathway
SRA
Endothelial cell or macrophage
B100
VLDL
E
CII
FFAs
Free cholesterol
Peripheral cell
Muscle, fat
Adrenals
Gonads
B
LDL receptor
LDL
B100
Triglyceride-rich VLDL remnant
E
Triglyceride/CE exchange by CETP
CE-rich HDL
LCAT
Small HDL
ABCAs
Free cholesterol
Peripheral cell cholesterol
potentially atherogenic cholesterol
C

Figure 2.6 Lipid transport and sites of drug action. (A) What happens to dietary lipids. (B) Transport of lipid from the liver to peripheral tissues. (C) Transport of lipid from peripheral tissues to the liver. ABCA, ATP-binding cassette transporter A; ACAT, acyl-CoA:cholesterol acyltransferase; CETP, cholesterylester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LCAT, lecithin–cholesterol acetyltransferase; LDL, low-density lipoprotein cholesterol; MTP, microsomal triglyceride transfer protein; SRA, scavenger receptor; VLDL, very-low-density lipoprotein cholesterol.

Why are increased LDL levels dangerous?

Increased LDL and apo B100 are risk factors for CVD, because excess LDL that is not taken up by tissues or the liver and cannot be removed by HDL pathways (below) undergoes lipid peroxidation to become modified LDL which becomes a ligand for alternative, scavenger receptor pathways (e.g. via steroid receptor RNA activator 1 – SRA1 (see Fig. 2.6B) or thrombospondin receptor CD_{36}) present on endothelial cells and macrophages. Oxidised lipoproteins (often the cholesterol esters in LDL or chylomicron remnants) within macrophages transform these into foam cells, the first phase of the atherosclerosis mechanism (Case 2.8).

How is lipid transported from peripheral tissues to the liver? (Fig. 2.6C)

This is through the apo A1 system, and concerns HDL. It is known as the reverse cholesterol pathway. HDL particles are formed in the plasma from the coalescence of phospholipid–apolipoprotein complexes. Free plasma cholesterol is transferred by ATP binding cassette transporter A1 (ABCA1) to these small, cholesterol-poor HDL particles and esterified by LCAT, which is bound to HDL, to cholesterol ester (CE). This enables HDL to accept more cholesterol and larger HDL particles develop which can be metabolised in one of two ways. The entire HDL particle can be removed from plasma, or its CEs can be exchanged with triglyceride in VLDL, mediated by cholesterol ester transfer protein. The CEs are returned to the liver via VLDL conversion to LDL and LDL liver reception. The triglyceride transferred to HDL is a substrate for LPL and HDL particles are condensed down again to their smaller form. When apo B100 is removed by the liver, reverse cholesterol transfer is complete.

What is the association between CVD and cholesterol?

As total cholesterol (TC) (and LDL) increases so does CVD risk, the relative risks being similar for those with and without CVD. CVD risk is principally determined by the concentrations of LDL and HDL and to a lesser extent by triglycerides. Lowering cholesterol by diet, drugs or other means decreases CVD risk. A 1 mmol/l decrease in LDL reduces coronary death risk by 11% in the first year, 24% in the second, 33% in the third to fifth and 36% in the sixth and subsequent years. Of course, lipoproteins are only one part of overall CVD risk (Case 2.7) but hypercholestrolaemia is the permissive factor that allows other risk factors to operate.

What is the average plasma TC concentration in the UK?

The average plasma cholesterol concentration in the UK is 5.9 mmol/l, much higher than the 4 mmol/l in rural China and Japan where heart disease is uncommon. Furthermore, there seems to be no lower limit of cholesterol at which coronary risk stops – although the relation become progressively steeper as cholesterol rises – and so it is rational to base desirable targets as those above which coronary risk seems unacceptably high. Most plasma cholesterol is present in LDL, with smaller amounts in VLDL and HDL making up the TC.

How would you investigate hypercholesterolaemia?

Investigation must be in the context of a detailed clinical assessment, and the likelihood of it being secondary or primary, and in the context of other risk factors. Fasting for 10 hours avoids the post-prandial contribution to plasma triglycerides.

Are there other ways of assessing dyslipidaemia as well as serum lipid profiles?

Computed tomography scan calcification scoring is one way of further assessing risk in asymptomatic people.

What are the common dyslipidaemias?

Elevation of TC and LDL has received most attention, particularly because it can be modified by lifestyle changes and drug therapies. The evidence showing that reducing TC and LDL can prevent CVD is strong, based on many randomised controlled trials. Several other types of dyslipidaemia predispose to premature CVD. A particular pattern, termed the atherogenic lipid triad, is more common than others, and consists of VLDL remnants manifested as mildly elevated triglycerides, increased small dense LDL particles, and reduced HDL levels. However, evidence is limited on the effectiveness and safety of intervening in this pattern to reduce CVD risk.

What do you know about risk levels and treatment targets?

Risk levels and assessment

The concept of total CVD risk is discussed in Case 2.7. If a person has a history of coronary heart disease, angina, stroke or transient ischaemic attack, peripheral vascular disease (includes carotid artery disease, aortic aneurysm), diabetes or a monogenic lipid disorder, risk assessment is unnecessary as they are already considered at high risk. Otherwise National Institute for Health and Clinical Excellence (NICE) guidelines recommend consideration of intervention for those with a 10-year risk ≥ 20%.

Treatment targets

NICE guidelines recommend 40 mg simvastatin (or drug of similar efficacy and cost) as part of the management strategy for adults over 40 who have a 20% or greater 10-year risk of developing CVD. There is no target level for TC or LDL for primary prevention; 40 mg simvastatin (or drug of similar efficacy and cost) should be offered to all adults with clinical evidence of CVD, increasing to 80 mg simvastatin or a drug of similar efficacy and cost if the TC does not fall to ≤ 4 mmol/l or the LDL does not fall to ≤ 2mmol/l.

How strong is the evidence for lipid-lowering therapy in reducing CVD risk?

The compelling evidence is with statins. The early major statin trials in people with established CVD using simvastatin and pravastatin (4S, CARE, LIPID) and in asymptomatic people at risk of developing CVD (WOSCOPS, AFCAPS/TEXCAPS) showed significant reductions in coronary events, coronary mortality and often all-cause mortality. A meta-analysis of these five trials showed significant reductions of major coronary events by 31%, coronary mortality by 29% and all-cause mortality by 21%. There was no difference in non-CVD mortality. Later statin trials with atorvastatin (GREASE, ASCOT, CARDS, PROVE-IT, TNT, IDEAL, 4D), fluvastatin (LIPS, ALERT), pravastatin (ALLHAT, PROSPER, PROVE-IT) and simvastatin (HPS, A to Z, IDEAL) extended the evidence base to many populations including older people, people with acute coronary disease, people with diabetes, renal transplantation, and in populations hitherto thought to have low TC and LDL concentrations (the Heart Protection Study randomised people with TC > 3.5 mmol/l). Trials looking specifically at women have been absent. Intensive dose statin trials (TNT, IDEAL, PROVE IT, A to Z) show conflicting results. The Cholesterol Trialists' Collaboration, in a meta-analysis of 14 statin trials with data from 90 056 patients, showed safe reduction in the 5-year incidence of major coronary events, coronary revascularisation and stroke by about one-fifth (21%) per mmol reduction in LDL, accompanied by decreased all-cause mortality; the linear decrease extends down to the current LDL targets of 2 mmol/l, and those with pre-treatment levels < 3mmol/l have the same relative risk reduction. Efficacy of different statins varies: at a maximum dose of 40 mg pravastatin reduces LDL by 29%, and at a maximum dose of 80 mg simvastatin, atorvastatin and rosuvastatin reduce LDL by 42%, 55% and 58%, respectively. Each doubling of statin dose produces a further 5–6% LDL reduction.

What lipid-lowering therapies are there?

Lipid-lowering therapies are summarised in Table 2.29.

- Drugs for treatment of hypercholesterolaemia include statins, bile acid sequestrants, cholesterol absorption inhibitors and nicotinic acid, and drug combinations include statins and cholesterol absorption inhibitors and statins and bile acid sequestrants.
- Drugs for treatment of hypertriglyceridaemia include fibrates (with substantial evidence of benefit), nicotinic acid and n-3 fatty acids. Mixed dyslipidaemia with elevated triglycerides and low HDL is common. The main strategy is still a statin to treat LDL to target.
- Drugs affecting HDL include statins, fibrates, nicotinic acid and cholesterylester transfer protein (CETP) inhibitors (e.g. torcetrapib, withdrawn because of risks).

Might statins work in ways other than lipid lowering?

Accelerated atherosclerosis in chronic inflammatory conditions such as rheumatoid arthritis is not explained by traditional risk factors. Such patients may have increased levels of a CD4 subset of T cells that lack CD28 expression called CD4 null cells, which can also be activated by infection and are more abundant in older people. These cells express interferon-γ and may cause a number of effects including endothelial cell death via engagement of their Toll-like receptor TLR2. TLR2 may be regulated by statins and there is evidence for endothelial stabilisation and regression of atherosclerosis with statin therapy, the anti-inflammatory effects of which are being examined in a range of non-CVD conditions including rheumatoid arthritis.

What is the clinical spectrum of statin-induced myopathy?

The spectrum includes: myalgia (painful muscles without elevated creatine kinase level), myositis (painful muscles with elevated creatine kinase level, generally up to 10× upper limit of normal), rhabdomyolysis (painful muscles with elevated creatine kinase level, generally over 10× upper limit of normal, often with compromised kidneys), and asymptomatic increase in creatine kinase level. The clinical features include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping, and tendon pain. Symptoms tend to be proximal, generalised, and worse with exercise.

What are the risk factors for statin-induced myopathy?

How statin myopathy arises is uncertain, but risk factors include age, female sex, low body mass index, vigorous exercise, comorbidity (diabetes, kidney disease, liver disease, hypothyroidism, intercurrent infection, surgery or trauma), drug interactions especially with drugs that are inhibitors or substrates of the cytochrome P450 pathway (e.g. fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, thiazolidinediones, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin), diet (excessive grapefruit or cranberry juice), alcohol and genetic factors (e.g. polymorphisms of the cytochrome P450 isoenzymes). Lipophilic statins (e.g. simvastatin, atorvastatin) are more likely to induce myopathy than hydrophilic ones (e.g. pravastatin, rosuvastatin).

Table 2.29 Lipid-lowering therapies

Class of drug	How they work	What they do	Compelling indications	Possible indications	Side effects and caution	Contra-indications
Statins, e.g. simvastatin, atorvastatin	HMG-CoA reductase inhibition – reduction in intracellular cholesterol induces LDL receptor expression on hepatocyte surface and increased extraction of LDL from blood	Lowers TC and LDL	Atherosclerotic CVD High CVD risk Diabetes	Lower CVD risk	Myopathy Type 2 diabetes Myopathy Rhabdomyolysis (dose-dependent) Liver disease Polyneuropathy Haemorrhagic stroke Type 2 diabetes Caution with non-alcoholic steatohepatitis, untreated hypothyroidism, significant kidney disease, excessive grapefruit juice (metabolised through P450)	Gemfibrozil (interferes with statin metabolism, increasing myopathy risk)
Bile acid sequestrants / anion exchange resins, e.g. cholestyramine, colestipol	Bind bile acids in intestine	Increase LDL receptor activity in liver Increase LDL clearance from plasma	None (poorly tolerated)	Inadequate LDL on statin and ezetimibe (e.g. familial hypercholesterolaemia) Cholestasis with itching	Gastrointestinal Exacerbation of hypertriglyceridaemia	Important interactions with many drugs
Cholesterol absorption inhibitors, e.g. ezetimibe	Blocks cholesterol absorption in the gut (most probably by interacting with the NPC1L1 protein on the brush border)	Lower LDL by 15–20% when added to diet or by 20–25% when added to diet with statin Long-term trial data awaited	With statin where LDL not at target despite maximum statin or tolerated statin dose Monotherapy in statin intolerance		Liver disease	None Well tolerated
Nicotinic acids		Reduce triglycerides and cholesterol	Severe hypertriglyceridaemia with prior acute pancreatitis Severe hypertriglyceridaemia not responsive to fibrates	With other lipid-lowering drugs, most often in mixed hyperlipidaemia	Flushing Caution in kidney disease, liver disease, diabetes, gout, peptic ulcer disease	Glucose intolerance
Fibrates, e.g. gemfibrozil	Modulation of nuclear receptors in various tissues (liver, muscle, fat)	Raise HDL Lower triglycerides	Type III hyperlipoproteinaemia Severe hypertriglyceridaemia (> 10 mmol / l) with risk of pancreatitis	Type 2 diabetes (specialist) Moderate to severe hypertriglyceridaemia with controlled LDL and very high CVD risk (specialist)	Caution in kidney disease	Statin (gemfibrozil interferes with statin metabolism)

Table 2.29 Lipid-lowering therapies—cont'd

Class of drug	How they work	What they do	Compelling indications	Possible indications	Side effects and caution	Contra-indications
Fish oils Omega-3 (n-3) fatty acids / acid ethyl esters: Eicosapentaenoic docosahexaenoic and alpha-tocopherol as Omacor 2–4 g / day Omega-3-marine triglycerides as Maxepa 5–10 g / day			Severe hypertriglyceridaemia (Maxepa) CHD prevention (Omacor)	Hypertriglyceridaemia	Caution in haemorrhagic disorders, diabetes and with anticoagulants	

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LDL, low-density lipoprotein cholesterol; TC, total cholesterol.

Should creatine kinase be measured before starting statin therapy and monitored during statin therapy?

Guidance differs. A reasonable compromise is to measure baseline creatine kinase before starting therapy in high-risk groups, but it is unclear what constitutes an acceptable rise in creatine kinase with statins. Slightly raised concentrations of creatine kinase are common in the general population. Physical activity, especially when unaccustomed, may also increase creatine kinase. Routine monitoring in asymptomatic patients is not generally recommended.

Should liver enzymes be checked in people on statin therapy?

Baseline transaminases are often checked when starting therapy. Routine monitoring is not necessary in the absence of symptoms. If transaminases are raised but less than three times the upper limit of normal, statins are not necessarily precluded.

How should we react to HDL levels on current evidence?

Low HDL (< 1.0 mmol/l in men, < 1.2 mmol/l in women) remains a strong independent risk factor for CVD. Levels may be improved by exercise and stopping smoking. High levels of HDL are often associated with elevated LDL. While the ratio of the two is often regarded as a useful index of CVD risk, a normal ratio in the setting of raised HDL and LDL has been shown to increase risk, and the efficacy of statins in the Heart Protection Study was independent of HDL levels. The combination effect of statins and torcetrapib may have additive effects on lowering LDL and raising HDL.

Is HDL cholesterol always good?

HDL-mediated reverse cholesterol transport is thought to be the major mechanism by which HDL protects against atherosclerosis, and plasma levels of HDL and apo AI are inversely proportional to CVD risk. Almost 40% of HDL variation between individuals is genetically determined, one-quarter of which is attributable to polymorphisms of the *CETP* gene. Lower CETP levels mean higher HDL levels (or at least higher levels of large, cholesterol-rich HDL). Evidence as to whether these mutations are protective is conflicting. Some studies have shown increased CVD risk. Adverse effects of CETP deficiency may be attributable to impairment of reverse cholesterol transport and loss of the antiatherogenic properties of HDL resulting from its increased cholesterol content and larger size. A few studies have even shown CVD reduction with increased HDL particle size.

Is hypolipidaemia a problem?

It may be secondary to malabsorption. Primary hypoalphalipoproteinaemia (low HDL) is a common correlate of hypertriglyceridaemia (prevalence 10–25%). Isolated low HDL due to, for example, *ABCA1* mutations, is very rare. Hypobetalipoproteinaemias are rare, but the very rare abetalipoproteinaemia with severe hypocholesterolaemia is associated with retinitis pigmentosa, fatty liver, acanthocytes and a Friedrich's ataxia-like syndrome. There is an uncertain but observational relationship between low cholesterol levels and cancer.

Does management differ in familial hypercholesterolaemia compared with common hypercholesterolaemia?

The possibility of familial hypercholesterolaemia should always be suspected, especially if the TC is > 7.5 mmol/l, which is typical in familial hypercholesterolaemia, and if there is a personal or family history of CVD. High-intensity statin therapy is needed to achieve a > 50% reduction in LDL, increasing to maximum tolerated doses. Ezetimibe is often needed additionally. Early referral to a cardiologist is important if coronary disease is suspected.

Is the benefit of statin therapy as clear for stroke as for coronary heart disease?

The correlation between cholesterol and stroke is less clear than for coronary heart disease, but statin therapy is recommended.

CASE 2.14 HYPERTENSION

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Thomas Roberts, aged 39 years
>
> Thank you for seeing Mr Roberts, who was diagnosed with hypertension 2 months ago at an insurance medical, urgently. Blood pressure then was 190/114 and baseline investigations revealed normal urinalysis, normal electrolytes and creatinine and a normal ECG. He did admit to occasional palpitations. His fasting blood glucose was normal and his cholesterol was 5.4 mmol/l. He was started on atenolol 50 mg and reviewed 1 month later, at which time blood pressure was 180/110 and amlodipine was added. He has noticed intermittent headaches and sweats since then, and blood pressure today is 200/120. I am concerned that there may be a secondary cause for his hypertension and that the headaches may represent worsening incipient complications.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Thomas Roberts is a 39-year-old solicitor recently diagnosed with hypertension at an insurance medical for a second mortgage as he and his wife were buying a new house for their expanding family of three children and two dogs. He has no past medical history of note but has seen his GP regularly over the last 2 months for first-line investigations (blood tests and electrocardiogram, which he has been advised are normal) and started treatment, initially atenolol, and now additional amlodipine. He has noticed occasional episodes of his heart racing over the last few months, which he has attributed to stress, and occasional sweats, which he has put down to being 'less fit than he used to be'. He has developed headaches since starting the amlodipine, and a small amount of ankle swelling. He is concerned about being on medication potentially lifelong and also being declined life assurance.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

The objectives when evaluating hypertension are: assessment for possible causes, assessment for target organ damage and planning of appropriate investigation and treatment. Referral to secondary care is indicated in the following circumstances:

- A need for urgent treatment, as in accelerated or malignant hypertension (blood pressure > 180/110 with papilloedema or retinal haemorrhage)
- Suspected phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor or diaphoresis)
- Other symptoms suggesting a secondary cause
- Young age (< 20 years or needing treatment < 30 years)
- Sudden onset or worsening hypertension
- Resistance to a multidrug regimen (three or more drugs) or problems with intolerance or multiple contraindications)
- Special situations such as unusual blood pressure variability, possible white-coat hypertension or pregnancy.

■ **Consider causes.** Most hypertension is 'idiopathic', a conspiracy of nefarious and poorly understood genetics and a rogue environment. Secondary causes are listed in Table 2.30.

Patient perspective

Explore his concerns about hypertension and its effects on life assurance for a mortgage.

Past medical history

■ **Consider target organs.** Possible target organ damage in hypertension is listed in Box 2.40.

Table 2.30 Secondary causes of hypertension

Secondary causes		Clinical clues
Renal		Haematuria Known history or family history of renal disease
Endocrine	Primary hyperaldosteronism (Conn's syndrome)	Consider in this patient's age group Symptoms rare, but may include tetany, muscle weakness and polyuria Sodium retention increases the extracellular fluid volume but water retention is usually insufficient for development of oedema
	Phaeochromocytoma	Sweats and palpitations Paroxysmal symptoms 90% have at least one of three symptoms: sweats, palpitations or anxiety Headaches The 10% 'rule' of these catecholamine-secreting tumours is that 10% are bilateral, 10% extra-adrenal, 10% malignant and 10% familial
	Cushing's syndrome	Unusual without other symptoms or signs
Aortic coarctation		Blood pressure discrepancy between right and left
Genetic		Defined genetic causes should be considered in young patients (e.g. aged 20) and include those in Box 2.41.
Drugs		

Box 2.40 **Possible target organ damage in hypertension**

- Cerebrovascular disease (history of transient ischaemic attacks or stroke)
- Coronary heart disease (history of angina or previous acute coronary syndrome, percutaneous coronary intervention or bypass grafting)
- Left ventricular hypertrophy or strain (electrocardiogram)
- Heart failure
- Renovascular disease (proteinuria or raised creatinine)
- Peripheral vascular disease (claudication)
- Aortic aneurysm in older patients
- Hypertensive retinopathy

■ **Consider risk factors for cardiovascular disease.** The usual suspects include age and sex, smoking, diabetes, cholesterol and family history. Contributory factors include excess weight, excess alcohol (> 3 units/day for men, > 2 units/day for women), excess salt, lack of exercise and environmental stress.

Drug and allergy history

Ask about drugs exacerbating hypertension. These include non-steroidal anti-inflammatory drugs, steroids and ciclosporin. Ask about possible side effects of antihypertensives (calcium channel blockers can cause headaches, flushing and ankle swelling).

Family history

Ask about renal disease (e.g. adult polycystic kidney disease).

Social history

Explore his concerns about hypertension and its effects on life assurance for a mortgage. A detailed social history, including alcohol intake and substance misuse (such as cocaine), is important.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ All hypertensive patients should have a thorough history and examination, urinalysis, serum creatinine and electrolytes, fasting blood glucose, lipid profile with a total cholesterol–high-density lipoprotein ratio (ideally fasted for evaluation of triglycerides) and an electrocardiogram.
- ◆ Further investigations in this case should include screening for Conn's syndrome, measurement of urinary catecholamines on three separate occasions to exclude phaeochromocytoma, measurement of thyroid function and possibly renal imaging and echocardiogram. While a renal cause is less likely with normal urinalysis, renal artery stenosis is possible and definitive exclusion would require computed tomography angiography or magnetic resonance angiography.
- ◆ This patient's headaches may be the result of amlodipine.
- ◆ Assure him that investigations will determine the optimum treatment and that, while hypertension needs to be declared in his application, it should not deny him life assurance.

Discussion

How would you investigate hypertension in a young person?

Hypertension warrants further investigations for secondary causes in young people (aged < 40 years), those with blood pressure resistant to treatment, and those with a family history of hypertension or stroke at age < 50 years. Before further investigations hypertension needs to be established by blood pressure measurements on at least three occasions (cuffs too small give false high readings); 24-hour ambulatory blood pressure measurement may be warranted.

Urinalysis, creatinine and electrolytes

These are essential to screen for hypokalaemia and renal disease. Only a third of patients with primary hyperaldosteronism exhibit frank hypokalaemia, although potassium concentrations in most are at the lower end of the reference range and sodium concentrations at the higher end, with hypokalaemic alkalosis common.

Electrocardiography, chest radiography and renal ultrasonography

Electrocardiography and chest radiography may show signs of left ventricular hypertrophy if hypertension is long-standing. With normal urinalysis and renal function renal parenchymal disease is unlikely and renal ultrasonography of limited benefit. None of these tests help to establish cause.

Measurement of plasma aldosterone and renin

Primary hyperaldosteronism is the most prevalent form of secondary hypertension, accounting for 5–10% of all hypertensive patients. Screening identifies a high plasma aldosterone concentration and usually markedly suppressed plasma renin activity in response to aldosterone-mediated volume increase, giving a high ratio of plasma aldosterone concentration to plasma renin activity (or a low ambulant or erect renin–aldosterone ratio). Exact cut-off values depend on the laboratory and assays used, a ratio of > 750 (aldosterone in pmol/l and plasma renin activity in ng/ml/h) with an absolute aldosterone concentration of > 400 pmol/l highly suggestive.

Antihypertensive drugs do not have to be stopped routinely before measurements (except for spironolactone, eplerenone and amiloride) but in some patients may contribute to false-positive and -negative results. Calcium channel blockers are suitable antihypertensives pre-investigation as they do not interfere with the renin–angiotensin–aldosterone system (RAAS).

Positive screening warrants confirmation of the diagnosis, usually by the observation that aldosterone fails to suppress with oral or intravenous sodium loading or a fludrocortisone suppression test (salt tablets, saline or fludrocortisone 0.2 mg daily for 5 days). Then to differentiate between the two principal causes – a unilateral aldosterone-producing adenoma (Conn's adenoma) and idiopathic hyperaldosteronism – selective adrenal venous sampling is the optimal test. Imaging is of limited value because of the high incidence of adrenal 'incidentalomas'.

24-hour urinary-free catecholamines or plasma-free metanephrines

Tumours that produce catecholamines, such as phaeochromocytomas and paragangliomas, are rare (0.1–0.6% of hypertensive patients), but important to exclude even if only mild headaches and no other classic symptoms (paroxysms of palpitations, sweating, and pallor) are present. Testing for plasma-free metanephrines is now the optimal test (sensitivity 99%, specificity 86%) but of limited availability and so screening is still predominantly based on excretion of urinary catecholamines (epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine, metanephrine, normetanephrine, and vanillylmandelic acid). False-positive test results can be prevented if the patient avoids consumption of caffeine, nuts, and chocolate for 24 hours before and during urine collection.

Renal imaging

Magnetic resonance angiography is the investigation of choice to exclude renal artery stenosis. In the absence of a renal artery bruit, it should be performed if screening tests for primary hyperaldosteronism and phaeochromocytoma are negative.

How may the RAAS contribute to the pathophysiology of hypertension?

Hypertension can result from raised peripheral resistance, excessive activation of the RAAS, excessive sympathetic nervous system activity or alteration in the balance of endothelial-derived vasoactive molecules. A range of genetic factors contributes. Renin is released from the juxtaglomerular apparatus of the kidney in response to low sodium or reduced renal perfusion. Renin converts angiotensinogen to angiotensin I (AI). AI is converted in the lung to angiotensin II (AII) by the action of angiotensin-converting enzyme (ACE). AII restores circulating volume via release from the adrenal cortex of aldosterone, which promotes sodium and water retention at the distal renal tubule in exchange for potassium and hydrogen, vasoconstriction and thirst. Aldosterone secretion is controlled almost exclusively by the RAAS and not by adrenocorticotrophic hormone. Numerous abnormalities of the RAAS can lead to hyperaldosteronism (Box 2.41).

How is phaeochromocytoma managed?

Clonidine suppression testing may be used for suspected phaeochromocytoma where urinalysis gives equivocal results. Where confirmed, phaeochromocytoma requires specialist management, including a search for the tumour with structural or functional imaging. Treatment with beta blockers is contraindicated without α-blockade (e.g. phenoxybenzamine) because unopposed α-blockade can cause severe vasoconstriction and pulmonary oedema; this is especially important perioperatively.

Why is hypertension important?

Hypertension is one of the most important preventable causes of premature morbidity and mortality.

How is hypertension defined?

Definitions are given in Box 2.42.

Box 2.41 Abnormalities in the renin–angiotensin–aldosterone system (RAAS)

Primary hyperaldosteronism

This is usually caused by an aldosterone-secreting adenoma (Conn's syndrome). Rarely it can result from bilateral hyperplasia or carcinoma. Renin production is suppressed.

Secondary hyperaldosteronism

This is hyper-reninaemic, usually in response to low sodium or reduced renal perfusion. The kidney perceives low circulating volume, which may be apparent as in renal artery stensois or true as in dehydration.

Pseudohyperaldosteronism (Liddle's syndrome)

This occurs when the sodium channel (ENac) in the tubule normally stimulated by aldosterone is switched permanently 'on' in the absence of aldosterone by an autosomal dominant mutation in its gene. Aldosterone levels are low, but renin is suppressed. Hypertension may respond to amiloride. Liddle's syndrome is one of a number of genetically determined causes of low-renin hypertension. Two others are glucocorticoid-remediable hypertension and apparent mineralocorticoid excess.

Glucocorticoid-remediable / suppressible aldosteronism (GRA)

Two closely related enzymes, 11β-hydroxylase and aldosterone synthase, normally coordinate synthesis of glucocorticoid and mineralocorticoid in the adrenal gland. In GRA a chimeric gene (autosomal dominant), comprising the aldosterone synthase gene with an upstream adrenocorticotrophic hormone (ACTH)-dependent promoter, results in expression of aldosterone synthase under ACTH regulation. Aldosterone levels are high and renin is suppressed. Hypertension may respond to dexamethasone, which suppresses ACTH.

Apparent mineralocorticoid excess (AME)

Normally an enzyme called 11β-hydroxysteroid dehydrogenase (11β-OHSD) within the renal tubules converts cortisol, which has a high affinity for the minerocorticoid receptor, to cortisone, which does not. In AME the *11β-OHSD* gene is mutated (autosomal recessive), leading to low enzyme activity and high cellular levels of cortisol, which can then act as a potent mineralocorticoid. Aldosterone levels are low, but renin is suppressed. Liquorice inhibits 11β-OHSD, exposing the mineralocorticoid and hypertensive potential. Hypertension may be treated with amiloride, spironolactone or dexamethasone suppression of cortisol synthesis, as dexamethasone is a less potent mineralocorticoid than cortisol.

Cushing's syndrome

Cushing's syndrome, especially that due to ectopic ACTH, mimics AME because high amounts of cortisol (which stimulates aldosterone) saturate its enzymatic conversion to cortisone (with little aldosterone activity).

Aldosterone deficiency (hypoaldosteronism)

This is due either to Addison's disease or to other conditions that damage the adrenal gland. Renin is elevated.

Aldosterone resistance

Resistance to aldosterone may be congenital (pseudohypoaldosteronism, in which ENac does not work) or acquired as a result of drugs (e.g. angiotensin-converting enzyme inhibitors, potassium-sparing diuretics such as spironolactone or amiloride) or renal tubular disease (e.g. systemic lupus erythematosus, amyloid, diabetes mellitus, obstructive uropathy).

Disorders of aldosterone deficiency or resistance are sometimes known as type 4 renal tubular acidosis.

See also Case 2.25, Table 2.56, for disorders of potassium related to aldosterone; Case 2.31, for renal tubular acidosis.

Box 2.42 Definitions of hypertension

Stage 1 hypertension

Clinic blood pressure is ≥ 140/90 mmHg and subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure is ≥ 135/85 mmHg.

Stage 2 hypertension

Clinic blood pressure is ≥ 160/100 mmHg and subsequent ABPM daytime average or HBPM average blood pressure is ≥ 150/95 mmHg.

Severe hypertension

Clinic systolic blood pressure is ≥ 180 mmHg, or clinic diastolic blood pressure is ≥ 110 mmHg.

How should blood pressure be measured?

Devices for measuring blood pressure must be properly validated, maintained and regularly recalibrated. An appropriate cuff size should be used. The environment should be standardised and relaxed, with the person quiet and seated, and their arm outstretched and supported. The radial or brachial pulse should be palpated before measuring blood pressure, since automated devices may not measure blood pressure accurately if there is pulse irregularity (e.g. atrial fibrillation) when blood pressure should be measured manually, using direct auscultation over the brachial artery.

Postural hypotension

In people with symptoms of postural hypotension (falls or postural dizziness) blood pressure should be measured either supine or seated, and again standing for at least 1 minute prior to measurement. If the systolic blood pressure falls by 20 mmHg or more when the person is standing medication should be reviewed and subsequent blood pressures measured standing with specialist investigation if symptoms of postural hypotension persist.

How is hypertension diagnosed?

Clinic blood pressure

Blood pressure is measured in both arms. If the difference in readings between arms is more than 20 mmHg, they should be repeated. If the difference in readings between arms remains more than 20 mmHg on the second measurement, subsequent blood pressures in the arm with the higher reading should be measured. If blood pressure measured in the clinic is ≥ 140/90 mmHg, a second measurement should be taken and if substantially different from the first, a third. The lower of the last two measurements should be recorded as clinic blood pressure.

Confirming the diagnosis

If clinic blood pressure is ≥ 140/90 mmHg, ambulatory blood pressure monitoring (ABPM) should be offered to confirm the diagnosis of hypertension. If a person is unable to tolerate ABPM, home blood pressure monitoring (HBPM) is a suitable alternative. While waiting to confirm the diagnosis, investigations for target organ damage and a formal assessment of cardiovascular risk should be obtained.

Severe hypertension

Antihypertensive drug treatment should be considered immediately, without waiting for results of ABPM or HBPM, for people with severe hypertension.

Specialist investigations

Referral to specialist care should be the same day if there is accelerated hypertension (blood pressure usually higher than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or suspected phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor and diaphoresis). Referral to specialist care should be considered in people with signs and symptoms suggesting a secondary cause of hypertension.

Using ambulatory or home blood pressure monitoring

ABPM requires at least two measurements per hour during usual waking hours, and the average value of at least 14 measurements taken during the person's usual waking hours to confirm the diagnosis. HBPM requires that: for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and seated; blood pressure is recorded twice daily, ideally morning and evening; blood pressure recording continues for at least 4 days, ideally for 7 days; measurements taken on the first day are discarded and the average value of all the remaining measurements used to confirm the diagnosis.

If hypertension is not diagnosed

Blood pressure measurement should be undertaken at least every 5 years, more so if clinic blood pressure is close to 140/90 mmHg. If there is evidence of target organ damage such as left ventricular hypertrophy, albuminuria or proteinuria, investigations for alternative causes of the target organ damage should be considered.

How are cardiovascular risk and target organ damage assessed?

A formal estimation of cardiovascular risk is needed to discuss prognosis and health-care options with people with hypertension, both for raised blood pressure and for other modifiable risk factors. Target organ damage assessment should include:

- Testing for the presence of proteinuria by a urine sample for estimation of the albumin–creatinine ratio and testing for haematuria using a reagent strip
- A blood sample to measure plasma glucose, electrolytes, creatinine, estimated glomerular filtration rate, serum total cholesterol and high-density lipoprotein cholesterol
- Examination of the fundi for the presence of hypertensive retinopathy
- A 12-lead electrocardiogram.

For people aged under 40 with stage 1 hypertension, specialist evaluation of secondary causes of hypertension and a more detailed assessment of target organ damage should be considered. This is because 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people.

What lifestyle interventions should be considered for hypertension?

These include: improving diet and exercise patterns; reducing alcohol consumption, stopping excessive consumption of coffee and other caffeine-rich products; keeping salt intake low; smoking cessation; relaxation therapies (evidence debatable).

How should antihypertensive drug treatment be initiated and titrated?

If possible, drugs should be taken once daily. Treatment for isolated systolic hypertension (systolic blood pressure ≥ 160 mmHg) should be the same as for both raised systolic and raised diastolic blood pressure. Treatment in people aged over 80 years should be the same as treatment for people aged 55–80 years, taking into account any comorbidities. An ACE inhibitor should not be combined with an angiotensin II receptor blocker (ARB). Management in pregnancy or breastfeeding is a specialised area. There are four treatment steps to consider (Fig. 2.7, Table 2.31).

How is treatment monitored?

Clinic blood pressure measurement should be used to monitor the response to treatment. For people identified as having a 'white-coat effect' – a discrepancy of more than 20/10 mmHg between clinic and average daytime ABPM or average HBPM blood pressure measurements at the time of diagnosis – ABPM or HBPM may be considered as an adjunct.

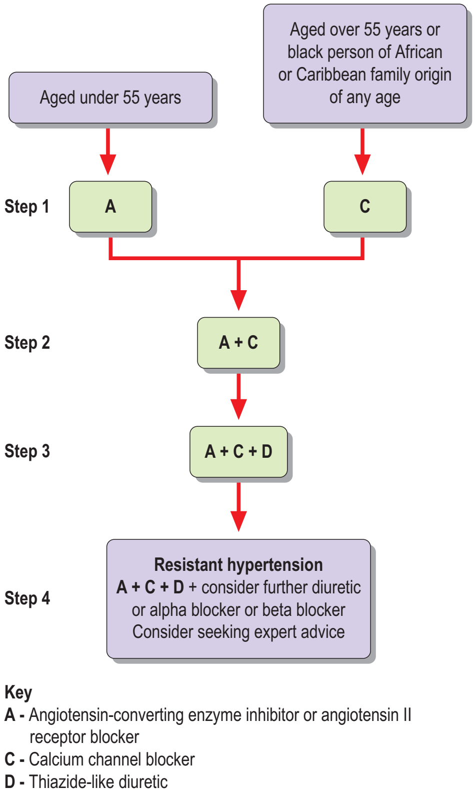

Aged under 55 years
Aged over 55 years or black person of African or Caribbean family origin of any age
Step 1
A
C
Step 2
A + C
Step 3
A + C + D
Step 4
Resistant hypertension
A + C + D + consider further diuretic or alpha blocker or beta blocker
Consider seeking expert advice
Key
A - Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker
C - Calcium channel blocker
D - Thiazide-like diuretic

Figure 2.7 Summary of antihypertensive drug treatment . (From National Institute for Health and Clinical Excellence 2011 CG 127 Hypertension, with permission.)

Box 2.43 **Blood pressure targets**

Clinic blood pressure

- People aged under 80 years: < 140/90 mmHg
- People aged over 80 years: < 150/90 mmHg

Daytime blood pressure average ambulatory blood pressure monitoring or average home blood pressure monitoring during the person's usual waking hours

- People aged under 80 years: < 135/85 mmHg
- People aged over 80 years: < 145/85 mmHg

What are the blood pressure targets?

These are outlined in Box 2.43.

What is the evidence for choice of antihypertensive therapy?

There is overwhelming evidence that lowering blood pressure reduces cardiovascular risk, in particular stroke and myocardial infarction. There is much debate about the concept of 'beyond blood pressure' whereby different drug classes are believed to be advantageous over and above their blood-pressure-lowering effects. This is certainly true for targeted patients (e.g. ACE inhibitors if there is diabetic nephropathy).

The HOPE trial analysed ramipril versus placebo in people at high risk of cardiovascular disease (CVD) events; 80% had known coronary disease. Average blood pressure was 139/79 mmHg at entry. Blood pressure reduction achieved was modest, 3.3/1.4 mmHg. In other words, for a very small blood pressure reduction there was a very large decrease in CVD events, promoting the notion of the added value of ACE inhibitors beyond blood pressure lowering. Risk reductions were as follows: myocardial infarction 20%, stroke 32%, CVD death 26%, all deaths 16%, new-onset diabetes 25%.

The LIFE trial compared losartan with atenolol in older hypertensive people with left ventricular hypertrophy and showed that for similar reduction in blood pressure the ARB produced better results with respect to stroke. On closer analysis it appears that this can be largely explained by ARB reduction of new-onset atrial fibrillation rates (33%).

The Blood Pressure Lowering Treatment Trialists' Collaboration 2003 meta-analysis assessed data from 29 trials involving 162 341 patients and concluded that there was no significant difference in cardiovascular events or mortality between ACE inhibitors, beta blockers, calcium channel blockers or diuretics. A caveat was that ACE inhibitors might have more benefits than other agents in stroke.

However, the ASCOT blood pressure trial was stopped early because of a reduction in all-cause mortality and additional cardiovascular and stroke benefits in favour of amlodipine and perindopril over atenolol and a thiazide. Amlodipine and perindopril did result in an overall slightly greater blood pressure reduction, suggesting again that blood pressure lowering is key. ASCOT impacted significantly blood pressure guidelines, which had previously recommended an AB/CD rule giving beta blockers equal weight with other agents.

It seems sensible to conclude that differences between treatment regimens can largely be explained by their blood-pressure-lowering effects. Beta blockers, while not preferred as initial routine therapy, are not ineffective but may merely be less effective than other agents. There may still be compelling indications for their use as first-line treatment (see Table 2.31), and they may be preferable in younger patients, for women of childbearing age, patients with increased sympathetic overdrive and patients intolerant of ACE inhibitors or ARBs. Refractory hypertension not responsive to modern prescribing occasionally may be tackled with centrally acting sympatholytics such as moxonidine or methyldopa, or vasodilators such as hydralazine.

Prescribing steps if no compelling indications or contraindications

These have been outlined (Fig. 2.7, Table 2.31).

Table 2.31 Antihypertensive treatment if no compelling indications or contraindications

Treatment step	Comments	Treatment
Step 1	This should be offered to: People aged under 80 with stage 1 hypertension and one or more of: target organ damage; established cardiovascular disease; renal disease; diabetes; 10-year cardiovascular risk equivalent to 20% or more. For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, specialist evaluation of secondary causes of hypertension and a more detailed assessment of potential target organ damage should be considered. People any age with stage 2 hypertension	People aged under 55 years should be offered an ACE inhibitor or ARB. People aged over 55 years and black people of African or Caribbean family origin of any age should be offered a CCB. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, a thiazide-like diuretic should be offered. If treatment with a diuretic is being started, or changed, a thiazide-like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily), is preferred to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. Beta blockers are not preferred in step 1. However, they may be considered for younger people if ACE inhibitors and ARBs are contraindicated or not tolerated or there is evidence of increased sympathetic drive, and for women of childbearing potential.
Step 2	If blood pressure is not controlled by step 1 treatment, step 2 treatment should be offered.	A CCB should be offered in combination with either an ACE inhibitor or an ARB. If a CCB is not suitable, a thiazide-like diuretic should be offered. For black people of African or Caribbean family origin, an ARB in preference to an ACE inhibitor should be considered, in combination with a CCB. If a beta blocker was used in step 1, a CCB rather than a thiazide-type diuretic should be added, to reduce the risk of diabetes.
Step 3	Before step 3 treatment, medication should be reviewed to ensure step 2 treatment is at optimal or best-tolerated doses.	An ACE inhibitor or an ARB should be offered in combination with a CCB and a thiazide-like diuretic.
Step 4	Clinic blood pressure that remains 140 / 90 mmHg or higher after step 3 treatment with optimal or best tolerated doses should be regarded as resistant hypertension. Step 4 treatment should be considered, with or without expert advice.	Further diuretic therapy with low-dose (25 mg once daily) spironolactone if blood potassium level is 4.5 mmol / l or lower (caution in people with reduced renal function) because of increased risk of hyperkalaemia. Further diuretic therapy with a higher dose thiazide-like diuretic if blood potassium level is higher than 4.5 mmol / l (with diuretic therapy blood sodium and potassium and renal function should be measured within 1 month and repeated as required). If further diuretic therapy is not tolerated or contraindicated or is ineffective, an alpha or beta blocker may be considered. If blood pressure remains uncontrolled with optimal or maximum tolerated doses of four drugs, expert advice is needed.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Compelling and potential indications and contraindications

In many, particularly older, patients there may be compelling reasons to choose or not to choose a drug that deviates from the prescribing steps. These are shown in Table 2.32.

What is the concern about ACE inhibitors and ARBs being used in combination?

In the ONTARGET trial of ramipril versus telmisartan versus both in reducing CVD death, myocardial infarction, stroke and hospitalisation for heart failure, there was no apparent benefit from both agents, despite a modest further reduction in blood pressure; the combination also provoked increased adverse effects such as syncope and increased need for dialysis. Renal outcomes in the ONTARGET study were similarly not beneficial for the combination of drugs. Further, in the TRANSCEND study of telmisartan in high-risk patients intolerant of an ACE inhibitor, there was no benefit seen from telmisartan. And so this creates an apparent puzzle: in HOPE, an ACE inhibitor was shown to be better than placebo; in ONTARGET, an ARB and an ACE inhibitor were shown to be equally effective; yet in TRANSCEND, an ARB was not shown to be better than placebo when an ACE inhibitor was not tolerated. The answer to this might lie in the fact that in the TRANSCEND group of high-risk patients a great deal of preventive treatment was already being applied and the ceiling of benefit had already been reached. The current best conclusions from this are that ACE inhibitors and ARBs have been shown to be equally effective, but that the combination of an ACE inhibitor and ARB is associated with more adverse outcomes without an increase in benefit and cannot be recommended. Likewise, direct renin blockers are unlikely to be superior to other RAAS blockers. It appears unwise to totally block the RAAS, which exists for a reason, such as keeping us upright!

Table 2.32 Choosing antihypertensive agents based if compelling or potential indications or contraindications

	Compelling indications	Possible indications	Caution	Compelling contraindications
Alpha blocker	Benign prostatic hypertrophy		Postural hypotension Heart failure as monotherapy	Urinary incontinence
ACE inhibitor	Heart failure Post myocardial infarction CVD Type 1 diabetes Secondary stroke prevention	CKD Type 2 diabetic nephropathy Proteinuric renal disease	Renal impairment Peripheral vascular disease	Pregnancy Renovascular disease
ARB	ACE inhibitor intolerance Type 2 diabetes Hypertension with LVH Heart failure in ACE inhibitor-intolerant patients Post myocardial infarction	LV dysfunction post myocardial infarction Intolerance of other antihypertensive drugs Proteinuric renal disease CKD	Renal impairment Peripheral vascular disease	Pregnancy Renovascular disease
Beta blocker	Angina, myocardial infarction	Heart failure	Heart failure (but increasingly used to treat heart failure under specialist supervision) Peripheral vascular disease Diabetes (except with CVD)	Asthma / COPD Heart block
Calcium channel blocker (dihydropyridine, e.g. amlodipine)	Elderly, isolated systolic hypertension	Angina		
Calcium channel blocker (rate limiting, e.g. diltiazam, verapamil)	Angina	Elderly patient	Combination with beta blocker	Heart block Heart failure
Thaizide-like / thiazide	Elderly, isolated systolic hypertension Heart failure Secondary stroke prevention			Gout (but thiazide occasionally necessary, with allopurinol)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVD, cardiovascular disease; LV, left ventricular; LVH, left ventricular hypertrophy.

Is isolated systolic hypertension (ISH) important in older people?

Left ventricular contraction unleashes an arterial pressure wave, which on meeting points of natural resistance such as vessel bifurcation produces a smaller backward pressure wave that is reflected back towards the aorta. This reflected wave is greater in states of arterial stiffness or arteriosclerosis, and indeed in ISH, and provides a general measure of fitness of the vascular tree. It increases aortic systolic pressure and reduces stroke volume and sets up, to an extent, a vicious cycle; arterial stiffness and increased pulse wave velocity increase systolic blood pressure with age.

ISH was once wrongly interpreted as a benign part of ageing, like greying hair, and it was thought that there was a J curve such that if systolic blood pressure fell below a certain point diastolic blood pressure would be so low as to compromise coronary filling during diastole. These were incorrect assumptions, and abundant evidence reveals a strong linear relationship between blood pressure and stroke risk.

Systolic blood pressure is the strongest predictor of CVD events in people over 40 years, and heart failure and CVD events are effectively prevented by treating ISH.

Neurological problems

CASE 2.15 HEADACHE

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Ms Deborah Good, aged 23 years
> Please see this young lady, who developed a severe headache over the weekend. I am concerned that it has not improved after 2 days and would appreciate your excluding serious causes before treating it as migraine. She is normally well and works at your hospital as a dietitian.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Ms Deborah Good is a 23-year-old dietitian who developed a sudden headache 2 days ago which has not improved and now she has been admitted to hospital. The headache came on suddenly during a night out drinking with friends and felt like something 'popping' at the back of her head. She has a history of migraine headaches for which she takes occasional sumatriptan or over-the-counter tablets. Her migraines usually evolve over a few hours, tend to be unilateral, usually left-sided but occasionally right, and associated with photophobia and nausea, but this headache was more sudden and did not respond to medication. Her migraine headaches have worsened recently because of work stresses and she has had almost daily headaches for the last 2 months. Her daily headaches are band-like across both temples and tend to be worse in the afternoon. She has taken more over-the-counter paracetamol, ibuprofen and codeine because of these. She does not sleep well and finds work tiring. She does not smoke and has never taken illicit drugs. She seldom drinks alcohol, but last weekend was an exception when she was 'drowning her sorrows' with friends. She is very afraid both of being admitted to the hospital where she works and of needles.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Elicit details of the headaches.** She probably has two or three different types of headache and it is important to elicit details for each. There are no diagnostic tests for any of the primary headache disorders and medication overuse headache, and the history is all-important (Box 2.44). The pattern of attacks is a very helpful pointer to diagnosis.

■ **Consider causes.** A knowledge of causes of headache (Box 2.45), exclusion of serious causes (Box 2.46) and appreciation that multiple types of headache often overlap is essential. One approach to making the diagnosis is to consider three questions:

- Is there a recognisable syndrome, such as migraine?
- Could it be a serious headache, such as a subarachnoid haemorrhage (SAH), meningitis or the result of raised intracranial pressure?
- Could there be an alternative diagnosis?

Patterns of headache are important. Acute single headaches could be the result of a first migraine, SAH or meningitis. Recurrent headaches could be migraine, tension-type headache or cluster headache. Dull headache increasing in severity is usually benign, but may be caused by medication overuse, the oral contraceptive pill,

Box 2.44 **Headache questions**

How many different headache types does the patient experience?

- Separate histories are necessary for each.

Time questions

- Why has the patient presented now?
- How recent in onset (days, weeks, months or years ago)?
- Frequency, and temporal pattern (especially distinguishing between episodic and daily or unremitting)
- Duration with or without treatment

Character questions

- Intensity of pain
- Nature and quality of pain (e.g. dull ache, lancing pain)
- Site and spread of pain, and and whether unilateral or bilateral
- Associated symptoms (e.g. nausea, vomiting or photophobia, aura, or focal neurological symptoms)

Cause questions

- Predisposing and/or trigger factors
- Aggravating (e.g. foods, work, sneezing, coughing, bending) and/or relieving factors (e.g. darkened room)
- Family history of similar headache

Response questions

- What does the patient do during the headache?
- How much is activity (function) limited or prevented?
- What medication has been and is used, and in what manner?

State of health between attacks

- Completely well, or residual or persisting symptoms?
- Concerns, anxieties, fears about recurrent attacks, and/or their cause

Box 2.45 **Causes of headache**

The International Classification of Headache Disorders, 2nd edition (ICHDII), revised by the International Headache Society in 2004, remains the international standard and is largely based on clinical features.

Primary headaches

1. Migraine, without or with aura
2. Tension-type headache, frequent or infrequent episodic, or chronic
3. Cluster headache and other trigeminal autonomic cephalgias, including paroxysmal hemicrania and short-lasting neuralgiform headache with conjunctival injection and tearing
4. Other primary headaches, including stabbing, cough, exertional and sexual (repeated attacks of short-lived pain associated with activity), hypnic headache (generalised headaches that wake the person from sleep, brief – 5–180 minutes – and may occur two or three times per night), primary thunderclap headache, hemicrania continua and new daily persistent headache

Secondary headaches

5. Headache associated with head and/or neck trauma including chronic post-traumatic headache
6. Headache attributed to cranial or cervical vascular disorders, including ischaemia, intracerebral haemorrhage, subarachnoid haemorrhage, giant cell arteritis, carotid or vertebral artery dissection and cerebral venous sinus thrombosis
7. Headache attributed to non-vascular intracranial disorders, including idiopathic intracranial hypertension and increased intracranial pressure from neoplasm and hydrocephalus
8. Headache attributed to a substance or its withdrawal, including acute alcohol-induced headache, carbon monoxide-induced headache, food-related headache and medication overuse headache from ergotamines, triptans or analgesics
9. Headache attributed to infection
10. Headache attributed to a disorder of homeostasis including hypoxia or hypercapnia, metabolic disturbance, fasting, arterial hypertension (including phaeochromocytoma) and hypertensive encephalopathy
11. Headache or facial pain attributed to disorder of cranium, neck, eyes (errors of refraction are overdiagnosed as causing headache), ears, nose, sinuses, teeth, mouth or other facial or cranial structures, including headache of cervical spine origin, acute sinus headache, acute glaucoma and optic neuritis with visual loss
12. Headache attributed to psychiatric disorder

Neuralgias and other headaches

13. Cranial neuralgias, central and primary facial pain and other headaches, including trigeminal neuralgia and occipital neuralgia
14. Other headache, cranial neuralgia, central or primary facial pain

Box 2.46 **Some serious causes of headache**

Warning features in the history

- Headache that is new or unexpected
- 'Thunderclap' headache (intense headache with abrupt or 'explosive' onset)
- Headache with atypical aura (duration > 1 hour, or including motor weakness)
- Aura occurring for the first time during use of combined oral contraceptives
- New-onset headache in a patient older than 50 years
- Persistent morning headache with nausea
- Progressive headache, worsening over weeks or longer
- Headache associated with postural change
- New-onset headache in a patient with a history of cancer
- New-onset headache in a patient with a history of human immunodeficiency virus infection

The reality is that intracranial lesions (subarachnoid haemorrhage, tumours, meningitis) are uncommon.

Subarachnoid haemorrhage (SAH)

The crucial step in the history is to establish how quickly the headache reached maximal intensity – a headache still increasing in severity after 15 minutes is unlikely to be a SAH (although it could still have a serious pathology, e.g. meningitis). For exactly how many minutes a headache may still crescendo and still be SAH is unknown, as is for how long a SAH headache may last, although most physicians would think SAH unlikely if it does not reach maximum intensity within a minute of onset and fully resolves within an hour or two. This said, International Headache Society guidelines warn that headache is not always of sudden onset, and neck stiffness may take some hours to develop. The headache of SAH is often described as the worst ever, but some patients are inclined to use such descriptive terms for migraine, and even 'explosive' features can occur with migraine ('thunderclap') but the serious consequences of missing SAH call for a low index of suspicion. In the elderly particularly, classical symptoms and signs may be absent.

Raised intracranial pressure due to structural lesions

Rarely do intracranial tumours produce headache until quite large (pituitary tumours an exception). Raised intracranial pressure may provoke morning headaches or exacerbation by coughing or bending. Epilepsy is a cardinal symptom. Neurological signs are usually present but slowly growing tumours, especially those in neurologically 'silent' areas of the frontal lobes, may produce subtle personality change. Heightened suspicion is appropriate in patients known to have cancer elsewhere, or a suppressed immune system.

Meningitis

Fever and neck stiffness usually accompany meningitis, in an obviously ill patient. Headache is nearly always progressive over hours or longer, generalised or frontal, perhaps radiating to the neck, and accompanied later by nausea and disturbed consciousness.

Box 2.46 Some serious causes of headache—cont'd

Giant cell (temporal) arteritis

New headache in any patient over 50 years of age should raise the suspicion of giant cell arteritis (Case 2.47).

Primary angle-closure glaucoma

Non-specific headache can be a symptom of primary angle-closure glaucoma, especially in older people.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension, formerly termed benign intracranial hypertension or pseudotumour cerebri, causes progressive headache, more common in obese young women. It is associated with intracranial hypertension, often characterised by any of papilloedema, an enlarged blind spot, a visual field defect or a sixth nerve palsy, together with increased cerebrospinal fluid (CSF) pressure (> 200 $\mathrm{mmH_2O}$ in non-obese, > 250 $\mathrm{mmH_2O}$ in obese). CSF chemistry and brain imaging are normal. Other disorders must be excluded, including venous sinus thrombosis, and the cause is uncertain although microthrombi (i.e. part of the venous sinus thrombosis spectrum) have been postulated. Headache relates closely to intracranial pressure and improves after withdrawal of CSF to 120–170 $\mathrm{mmH_2O}$.

Cerebral venous sinus thrombosis (CVST)

Although uncommon, CVST is an important cause of headache. Predisposing factors include pregnancy, prothrombotic states, dehydration and sepsis, especially intracranial. Headache is usually generalised and acute or subacute. There may be signs of raised intracranial pressure, meningism, altered consciousness, seizures (often focal) and focal neurological deficit due to stroke (venous infarct). A non-contrast computed tomography (CT) scan in the acute phase may show an 'empty delta' sign and hyperintensity in the sagittal, straight and transverse sinuses. CT or magnetic resonance venography is useful. Initial treatment is with heparin followed by warfarin, duration dependent on persistence of the underlying cause. Secondary intracranial venous haemorrhage is common and does not necessarily contraindicate anticoagulation.

Carbon monoxide poisoning

Carbon monoxide poisoning is an uncommon but avoidable (and easily overlooked) cause of ill-health and fatalities. Symptoms include headaches, nausea, vomiting, giddiness, muscular weakness, dimness of vision and double vision. In suspected cases, domestic gas appliances should be checked (gas flames should burn blue, not yellow or orange). Measurement of blood carboxyhaemoglobin concentration shortly after exposure confirms the diagnosis.

idiopathic intracranial hypertension, neck disease, giant cell arteritis or tumour. A dull, unchanging headache may be a chronic tension-type headache or a result of depression.

Patient perspective

Explore any concerns she may have about the cause of the headache and appreciate her fear of being admitted to her workplace and of needles.

Past medical history

Migraine

Patients with migraine typically have recurrent episodic moderate or severe headaches (which may be unilateral and/or pulsating) lasting part of a day or up to 3 days, associated with gastrointestinal symptoms, during which they limit activity and prefer dark and quiet. They are well between attacks. Diagnostic criteria for *migraine without aura* are given in Box 2.47. It is easy to regard these as a checklist, but they require clinical interpretation, and all important is the pattern of occurrence of attacks.

Migraine with aura affects about one-third of migraine sufferers, but visual blurring and 'spots' are not diagnostic. Symptoms of typical aura are progressive, last 5–60 minutes prior to headache, and are visual, consisting of transient hemianopic disturbance or a spreading scintillating scotoma (patients may draw a jagged crescent). In some cases visual symptoms occur together or in sequence with other reversible focal neurological disturbances such as unilateral paraesthesia of hand, arm or face (the leg is rarely affected) and/or dysphasia, all manifestations of functional cortical disturbance of one cerebral hemisphere. Particularly in older patients, a typical visual migrainous aura may occur without any further development of a migraine attack. When there is a clear history of earlier migraine with similar aura, this is not alarming, but transient ischaemic attack is in the differential diagnosis. Patients may have attacks of migraine with and migraine without aura and may, over a lifetime, change from a predominance of one subtype to the other. Prolonged aura, especially persisting after resolution of headache or involving motor weakness, requires investigation. A very small number of families express recognised genes for familial hemiplegic migraine. Migrainous headache occurring every day (*chronic migraine*) is classified as a complication of migraine.

Box 2.47 Diagnostic criteria for migraine without aura

A At least five attacks fulfilling criteria B–D

B Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)

C Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality (i.e. varying with the heartbeat)
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia

E Not attributed to another disorder

Recently recognised features of migraine include cutaneous allodynia (tender skin / face / scalp) and autonomic symptoms such as nasal stuffiness.

Tension-type headache (TTH)

Episodic tension-type headache also occurs in attack-like episodes, is variable, often very low frequency and mostly short lasting – no more than several hours. Headache can be unilateral but is more often generalised. It is typically described as pressure or tightness, like a tight band around the head (non-pulsating), and commonly spreads into or arises from the neck. Whilst it can be disabling for a few hours, it lacks the specific features and symptom complex of migraine (although photophobia and exacerbation by movement are common to many headaches). TTH may be stress related or associated with functional or structural cervical or cranial musculoskeletal abnormality. *Chronic tension-type headache* occurs on > 15 days a month, and may be daily, and is disabling. Both migraine and TTH are aggravated by stress and, in practice, the distinction is not always easy and the two may coexist.

Cluster headache

In the trigeminal autonomic cephalalgias, daily occurrence of headache (often several attacks daily) is usual. The most common is cluster headache. This affects mostly men in their twenties or older and very often smokers. Typically (although there is a chronic subtype) headaches occur in bouts for 6–12 weeks, once a year or 2 years, often at the same time each year. The pain is intense, and strictly unilateral. Although focused in one or other eye, it can spread over a larger area of the head. Typically it occurs daily, at a similar time each day, often at night, 1–2 hours after falling asleep. Associated autonomic features of ipsilateral conjunctival injection and lacrimation, rhinorrhoea or nasal blockage, and ptosis as a partial Horner's syndrome, may be present.

Medication overuse headache (MOH)

It is estimated that 1 in 50 adults suffer from MOH. Combination analgesics containing barbiturates, caffeine and codeine are the prime candidates for analgesia-induced MOH, but even simple analgesics such as aspirin and paracetamol are implicated. Whilst the mechanism is again unclear, it is different from those of ergotamine intoxication and triptan-induced MOH, probably involving changes in neural pain pathways. Consequently, it may take a long time (weeks to months) for the headache to resolve after withdrawal.

Drug and allergy history

Medication overuse headache is caused by a wide range of analgesics, which paradoxically exacerbate symptoms when used regularly.

Family history

A family history of migraine is common. Any family history of sudden unexplained death or confirmed aneurysmal leaks is important to elicit.

Social history

Ask about stresses at work and at home. Migraine can disrupt social life and employment to a great extent.

SUMMARY BOX – ASSESSMENT AND PLAN

- She probably has a combination of tension-type headache (TTH) and alcohol withdrawal headache on a background of migraine and stress. The primary headaches are generally diagnosed on history (examination usually unrevealing except in cluster headache during attacks); the purpose of examination is debated, but the optic fundi should always be examined, blood pressure measurement is recommended (raised blood pressure is very rarely a cause of headache but patients often think it is), and examination of the head and neck for muscle tenderness (generalised or with tender 'nodules'), stiffness, limitation in range of movement and crepitation is often revealing, especially in TTH. Investigations, including neuroimaging, do not contribute to the diagnosis of migraine or TTH.
- A small subarachnoid haemorrhage cannot be excluded here and needs to be excluded by computed tomography brain scan and possible lumbar puncture, being sensitive to her fear of needles.

Discussion

How are migraine attacks prevented and treated?

Predisposing factors include stress, depression, menstruation, menopause and head or neck trauma. Trigger factors include relaxation after stress, especially at weekends or on holiday, and other changes in habit such as missing meals, missing sleep, lying in late, long distance travel, bright lights and loud noise (both perhaps stress inducing). Specific foods are less commonly implicated in triggering migraine than is widely believed, and most migraineurs can eat whatever they like as long as they keep up with their energy demands. A few susceptible individuals note a definite relationship between certain foods, or alcohol, and migraine. The foods may not always trigger an attack but tip the balance when the person is vulnerable. There is no case for blanket avoidance of cheese, chocolate, caffeine or citrus fruit (the four 'C's that used to be implicated as migraine triggers). Cravings for sweet or savoury foods are probably premonitory symptoms heralding the headache, not triggers. Too much and too little sleep can both play a role. Migraine is three times more common in women and hormonal factors (including the oral contraceptive pill or hormone replacement therapy) may be a cause. Strenuous exercise can precipitate an attack in a person unaccustomed to it. This puts many people off exercise, but regular exercise may help prevent migraine attacks by improving blood sugar balance, helping breathing, stimulating endogenous natural pain killers and promoting a general sense of well-being.

Treatments include aspirin, non-steroidal anti-inflammatory drugs and triptans, in stepwise fashion. Higher dose aspirin (600–900 mg) is needed, dispersible, and treatment should often be combined with an anti-emetic to reduce gastric stasis. The benefits of ergotamine are thought to be mediated by agonist activity at the serotonin 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors and triptans are pure agonists of these without the side effects of ergotamine, which acts at other receptors such as 5-HT$_2$. The pharmacological and clinical differences between sumatriptan, zolmitriptan, rizatriptan and probably eletriptan seem small, but naratriptan, almotriptan and perhaps frovatriptan have longer duration of action and sometimes delayed onset of action and a lower incidence of short-term side effects and a lower recurrence rate. Triptans are contraindicated in hypertension and vascular disease. Side effects include paraesthesia and myalgia. Sumatriptan and zolmitriptan are available as nasal sprays and are suitable where vomiting is a major migraine feature.

Beta blockers (propranolol or atenolol) are the prophylactic treatment of choice in patients without asthma. Amitriptyline may also be used first line. Second-line treatments include topiramate as a well-tolerated, effective strategy, and sodium valproate. Gabapentin may be tried third line. Methysergide, pizotifen and clonidine are now used much less frequently. It is recognised that a subtle persistently patent foramen ovale can cause migraine and this can be closed.

Is migraine linked with adverse vascular events?

Migraine with aura is associated with adverse vascular events including an increased risk of ischaemic stroke, angina and myocardial infarction; genetic polymorphisms predisposing to both migraine with aura and vascular events are likely to play only a small role in explaining the association. These associations appear to depend upon the underlying vascular risk status as measured by the Framingham cardiovascular disease (CVD) risk score. Migraine with aura is associated with an unfavourable CVD risk profile; intriguingly, however, a major study on women with migraine revealed that migraine with aura is only associated with stroke in women at low CVD risk and only associated with cardiac events in women at high CVD risk.

Migraine with aura is underpinned by cortical spreading depression, a wave of excitation followed by a wave of inhibition that progresses at a rate of 3 mm/s, and is both a neuronal and glial event. During this process, cortical blood flow rises then falls in response to brain metabolic changes, through the mechanism of cerebral autoregulation. Blood flow seldom falls below the ischaemic threshold, but cascades of mediators are released that may damage blood vessels and brain parenchyma, which may contribute to immediate or delayed stroke. Migraine with aura appears to cause widespread endothelial dysfunction and platelet activation and its effects appear to be greater on cerebral than on cardiac circulation.

Migraine now appears to be a systemic disorder that affects the vasculature and may be associated with reduced endothelial progenitor cells, a surrogate marker for impaired vascular function. Even in the absence of CVD risk factors, people with migraine have decreased cerebral and peripheral vascular resistance, and increased likelihood of retinal microvascular signs, hypercoagulability and inflammation. It is plausible that the biological mechanism by which migraine with aura causes cerebrovascular events requires a vasculature not impaired by atherosclerosis, whereas the effect of migraine with aura on coronary arteries might involve two mechanisms, one involving a normal vasculature and the other involving impaired vasculature. Further, the overall reducing prevalence of migraine that occurs in ageing may reflect impaired vasculature.

It is not clear whether treating and preventing migraine attacks reduces vascular risks. It may be important to modify traditional CVD risk factors for people with migraine with aura, which should lower the relative and absolute risk of myocardial infarction in migraine with aura. In contrast, however, since the relative risk of stroke associated with migraine with aura is highest in those at low CVD risk, modifying traditional CVD risk factors is unlikely to influence the relative risk of stroke, although it might reduce absolute risk.

How are cluster headaches and other trigeminal autonomic cephalgias treated?

Effective analgesia is difficult, but treatments include oxygen, subcutaneous sumatriptan or nasal sumatriptan or zolmitriptan, verapamil, lithium, gabapentin and corticosteroids.

How is a SAH diagnosed?

Thunderclap headache is a worrying symptom, commonly with photophobia and neck stiffness but without focal neurological signs. Non-contrast computed tomography (CT) detects over 90% of SAH if performed in the first 12 hours after onset of symptoms, but sensitivity decreases thereafter due to cerebrospinal fluid (CSF) flushing, or if a small bleed is suspected. In those with a SAH, detection rates on CT are 90% at 24 hours, 50% at 7 days and 20% at 9 days. This is why CSF sampling is so important. Lumbar puncture is mandatory if CT is negative and the history is typical, although many patients will have normal CSF (thunderclap headache). Lumbar puncture should be performed after 12 hours from the onset of symptoms and the use of spectrophotometry should be used to detect xanthochromia. Appropriately timed CT and lumbar puncture reliably exclude SAH, without need for angiography. Magnetic resonance also reliably detects SAH, but not until later. Acutely fluid-attenuated inversion–recovery imaging may be used, and subacutely T1-weighted images may be used; these detect 80% of SAH in days 4–14, and almost 100% thereafter.

What is xanthochromia?

Net bilirubin absorption (NBA) is calculated from spectrophotometric scanning. Xanthochromia is caused by the presence of bilirubin in the sample from the breakdown of red blood cells. Phagocytosis of the red cells releases oxyhaemoglobin (oxyHb), which is converted to bilirubin *in vivo* in a time-dependent manner. False positives may be the result of increased CSF protein or jaundice and results may be interpreted as follows:

- No significant NBA and no oxyHb – no evidence of SAH
- No significant NBA but oxyHb present – SAH very unlikely and bloody tap possible (the absence of bilirubin in the presence of oxyHb suggests that red cells are fresh and have not yet broken down, which is not the case in SAH provided that a lumbar puncture has been performed after 12 hours); discuss with neurosurgeons if there are clinical concerns
- NBA present and no oxyHb – may be the result of jaundice (if serum bilirubin normal and CSF protein low then SAH is likely, usually in those presenting a week after symptom onset; if serum bilirubin is high then SAH is likely if the adjusted NBA is high and jaundice is probable if it is low and oxyHb is absent)
- NBA and oxyHb present – SAH very likely.

How is SAH managed?

Most SAHs occur in or around the circle of Willis but this is not invariable, although it does mean that, for example, an anterior bleed on CT might be more likely to be due to an arteriovenous malformation (AVM). A positive CT should be followed by CT angiography to determine if the bleed represents a SAH or an AVM. If it does represent one of these, the next step is intervention. If it does not, the next step is digital subtraction angiography to try to confirm SAH or AVM. If positive, intervention should proceed. If negative, the question is whether or not there is a perimesencephalic distribution SAH. Re-bleeding is around 25% in the first 2 weeks and 50% in the first 6 months post-SAH, and thereafter around 3% annually. Coils or endovascular treatment, or neurosurgical clipping, may be used, and a coil plus stenting may also alter the flow dynamics that would otherwise keep the aneurysm open. The risk of vasospasm relates largely to the size of the bleed, rather than to manipulation.

List some causes of headache and fever

- Meningitis (bacterial or viral)
- Encephalitis
- Cerebral abscess
- Otitis media
- Mastoiditis
- Non-specific symptom of infection elsewhere, e.g. pneumonia, sinusitis, tonsillitis
- Non-infectious causes, e.g. SAH, cerebral venous sinus thrombosis, giant cell arteritis, pontine haemorrhage

List some warning signs in meningococcal disease

Warning signs of impending shock, respiratory failure or raised intracranial pressure in meningococcal disease are listed in Box 2.48. Most of these would be contraindications to lumbar puncture.

Box 2.48 **Warning signs in meningococcal disease**

- Rapidly progressive rash
- Respiratory rate < 8 or > 30 breaths per minute
- Poor peripheral perfusion, capillary refill time > 4 seconds, oliguria or systolic blood pressure < 90 mmHg (hypotension often a late sign)
- Heart rate < 40 or > 140 beats per minute
- Acidosis (pH < 7.3 or base excess > –5)
- White cell count < 4 × 10^9/l
- Markedly depressed (Glasgow Coma Score (GCS) < 12 or fluctuating (decrease in GCS > 2)) level of consciousness
- Focal neurology
- Persistent seizures
- Papilloedema

What are the findings of a normal CSF examination?

Fluid is clear with a normal pressure of 8–16 cmH_2O, fewer than five lymphocytes, a protein concentration of 0.1–0.45 g/l and a glucose concentration more than 50% that of blood glucose.

Should patients with suspected bacterial meningitis be scanned before lumbar puncture?

There is no evidence for this, and CT scanning is not reliable in excluding raised intracranial pressure. Generally, patients with suspected meningitis do not need neuroimaging prior to lumbar puncture, but indications to do so include diagnostic doubt (e.g. sudden headache and suspected intracranial haemorrhage), signs of raised pressure (e.g. severe vomiting, papilloedema), focal neurology, impaired consciousness or seizures.

What is the treatment of choice for bacterial meningitis?

The most common causes of community-acquired bacterial meningitis are *Neisseria meningitides* and *Streptococcus pneumoniae*. Cefotaxime 2 g 6-hourly or ceftriaxone 2 g 12-hourly with vancomycin and/or rifampicin for suspected penicillin-resistant meningococci are recommended in the UK where third-generation cephalosporin resistance to *S. pneumoniae* is less prevalent. Adults over 55 years of age and anyone at risk (e.g. soft cheese consumers) should also receive amoxicillin 2 g 4-hourly as *Listeria monocytogenes* is possible. Brain imaging is not necessary in most cases initially. Dexamethasone is now given with antibiotics unless there are contraindications.

When might you scan a patient with a headache?

Indications for neuroimaging are given in Box 2.49.

Box 2.49 **When to scan a patient with a headache**

- First or worst headache, particularly of sudden onset
- Headaches of increasing severity or frequency
- Increasing frequency of vomiting or headache on waking
- Headache triggered by coughing or straining or change in posture (although many headaches are worse with these, including sinusitis)
- Persistent symptoms or signs after attacks
- Meningism, confusion, impairment of consciousness or seizures

CASE 2.16 TRANSIENT ISCHAEMIC ATTACK

Candidate information

Role

You are a doctor in a rapid access transient ischaemic attack (TIA) / stroke clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Jack Middleton, aged 72 years
>
> Thank you for seeing Mr Middleton, who last week experienced an episode of expressive dysphasia. It lasted around 5 minutes. His vision, hearing and limb movements were unaffected. He is in sinus rhythm and blood pressure is currently around 160 / 90 mmHg. He takes amlodipine for hypertension. I would appreciate assessment in your rapid access stroke clinic.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Jack Middleton is a 72-year-old man who last week had an episode of being unable to talk. He could hear what others were saying and knew how he wished to reply, but could not speak words which expressed his thoughts, or, if he began to, could not complete his sentences and found himself substituting incorrect words. It lasted around 5 minutes. He is usually well apart from high blood pressure, for which he takes amlodipine. He has also had two episodes in which his right hand became 'clumsy', during which he was unable to do up his shoelaces or grip objects properly. He is very concerned about the speech loss and weakness because he is a composer who not only plays piano but lectures on music.

Box 2.50 **Symptoms of transient ischaemic attacks (TIAs)**

Symptoms attributable to a TIA relate to a specific area of the brain. Loss of consciousness, syncope and confusion do not have a focal origin and are *not* suggestive of a TIA. Diagnosing a TIA remains largely clinical and the following features are characteristic:

- Symptoms are almost invariably of *sudden onset.*
- The deficit tends to be *maximal at the onset* with progressive resolution over minutes or hours.
- Attacks are *self-limiting.*
- Symptoms are characteristically '*negative*', e.g. loss of movement, rather than unwanted movement.
- Symptoms are *attributable to focal areas of brain* such as motor cortex or language areas. *Anterior circulation TIAs* may produce weakness or sensory symptoms in the contralateral upper limb, lower limb or face, dysphasia (especially dominant hemisphere, usually left) or amaurosis fugax. *Posterior circulation TIAs* may produce diplopia, ataxia, dysphagia, unilateral or bilateral weakness or sensory symptoms but usually more than one symptom.
- Most patients do not experience significant headache but mild headache can occur. Severe headache during the attack should prompt an alternative diagnosis.
- Loss of consciousness is highly unusual (perhaps 1 : 1000 to 1 : 10 000 patients), and almost always the result of a small proportion of basilar TIAs that disturb consciousness centres. It is surprising how frequently loss of consciousness or confusion remain cited as 'probable TIA' or 'probable stroke' in hospital admissions. It appears to be a myth that is hard to dispel.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Elicit details of symptoms.** Establish handedness. The dominant hemisphere is usually the left, in right-handed individuals. Around 50% of left-handed individuals have a dominant right hemisphere. Then elicit details of symptoms (Box 2.50).

■ **Consider other conditions that can produce focal neurological symptoms:**

- Migraine (particularly acephalgic)
- Focal seizure or focal weakness (Todd's paresis) following a seizure
- Intracranial space-occupying lesion (haemorrhage, tumour)
- Metabolic disturbances (usually global)
- Demyelination.

Patient perspective

Assure him that your purpose is to prevent further attacks. Tell him that his GP was very correct to arrange urgent referral because TIAs or 'mini-strokes' are possible warning signs of a more significant stroke, but that the risk can be markedly reduced with prompt investigation and appropriate treatment. Explain that a TIA or 'mini-stroke' is usually the result of a small blood clot or a piece of fatty material that has broken off into the circulation.

Past medical history

TIAs are usually caused by atherosclerosis or emboli. Most people with TIAs are riddled with risk factors, such as hypertension (the single biggest risk factor for stroke) or atrial fibrillation.

Drug and allergy history

Ask about previous treatment for hypertension and any intolerance of drugs.

Family history

A family history is seldom relevant.

Social history

This is very important, particularly with respect to smoking, although in a rapid access stroke clinic it often gives way to the pressing arrangement of urgent investigations.

Discussion

Which investigations would you recommend for a patient following a suspected TIA?

Investigations are best undertaken via a rapid access TIA/stroke clinic but high-risk patients who may warrant immediate admission to hospital include those with crescendo TIAs. Investigations are directed at establishing a predisposing cause (Tables 2.33, 2.34).

SUMMARY BOX – ASSESSMENT AND PLAN

- The diagnosis is left anterior circulation transient ischaemic attacks (TIAs).
- Brain imaging may not be necessary with a single brief episode, unless there are features of concern such as headache or a history of malignancy or if TIAs have recurred in a short time frame.
- Carotid duplex imaging is indicated urgently.
- A 24-hour electrocardiogram recording is desirable to look for paroxysmal atrial fibrillation (PAF).
- An echocardiogram may be indicated if there are murmurs or if a mural thrombus is possible (e.g. recent myocardial infarction).
- Antiplatelet therapy is indicated, substituted by warfarin if an embolic source is discovered (usually PAF, less commonly mural thrombus).
- Statin therapy (simvastatin 40 mg) is almost invariably indicated.
- Blood pressure should be vigorously controlled (after a stroke treatment is usually not manipulated for 14 days but it should be controlled quickly after a TIA).

How does carotid stenosis cause TIAs?

While dislodged fatty atheromatous material, particularly prevalent in smokers, was traditionally thought to be the major mechanism, evidence now suggests that the mechanism from such atheromatous plaques is the same as that in coronary syndromes; a plaque may rupture, fissure or erode, triggering platelet aggregation and formation of

Table 2.33 Routine investigations following a transient ischaemic attack (TIA)

Investigation	Indications	Reason
Blood tests – full blood picture, urea and electrolytes, glucose, lipid profile, coagulation profile	All patients	Exclude diabetes Assess lipid profile
Electrocardiogram	All patients	Exclude atrial fibrillation or recent myocardial infarction
Carotid duplex imaging	All patients with anterior circulation symptoms, including amaurosis fugax, who would be considered fit for endarterectomy	Exclude surgically relevant carotid stenosis on appropriate side
24-hour electrocardiogram	Many patients (especially if history of palpitations)	Exclude paroxysmal atrial fibrillation
Echocardiography	Multiterritory symptoms Recent myocardial infarction Atrial fibrillation (if cardioversion might be contemplated) Murmurs Heart failure Young patients (especially if history of or suspected venous thromboembolism)	Exclude mural thrombus Assess left atrial size and assess for thrombus Exclude endocarditis if additional features raise suspicion (transoesophageal echocardiography if cardiac origin strongly suspected but not confirmed by transthoracic echocardiography) Exclude significant hypokinesis Exclude patent foramen ovale
Brain imaging	Prolonged TIAs Features of concern, e.g. headache, history of malignancy	Exclude bleed Exclude tumour Exclude arteriovenous malformation

Table 2.34 Selected investigations following a transient ischaemic attack (TIA)

Investigation	Indications	Purpose
Erythrocyte sedimentation rate C-reactive protein Temporal artery biopsy	Headache (older patients)	Exclude giant cell arteritis
Autoimmune screen Vasculitis screen	Other symptoms or signs suggesting autoimmune disease Raised inflammatory markers	Exclude systemic lupus erythematosus Exclude primary systemic vasculitis (seldom causes TIAs)
Thrombophilia screen	Young patient	Exclude antiphospholipid syndrome (protein C deficiency, protein S deficiency, activated protein C resistance and antithrombin III deficiency usually associated with venous and not with arterial thrombosis)
MR or CT angiography	History of trauma Progressive or 'crescendo' symptoms	Exclude carotid or vertebral dissection
CT angiography of aortic arch	TIAs (recurrent) in posterior circulation or same hemi-territory	Exclude significant aortic arch atheroma
CT angiography of thorax	Sensory symptoms in arm with arm raised above head Cervical rib on chest X-ray	Exclude thoracic outlet syndrome
Echocardiogram (with 'bubbles')	History of venous thromboemolism No TIA risk factors, and normal carotid imaging	Exclude patent foramen ovale or other right-to-left shunt

CT, computed tomography; MR, magnetic resonance.

thrombus, which leads to local occlusion or distal embolisation. Cap thickness in ruptured carotid plaques is generally thicker than ruptured coronary plaques, but rupture is still associated with relatively thin caps with dense macrophage infiltration.

Why do recurrent TIAs often give rise to identical symptoms?

Recurrent TIAs often have similar characteristics, implying that the same area of brain is rendered ischaemic. The cause is usually recurrent atherosclerotic embolism and emboli must therefore tend to lodge in the same small artery recurrently. As the point of origin of an embolus is far from its final lodging place, and with a potentially large number of other small arteries to choose from, the question of how so many emboli reach the same artery is at first intriguing. The probable explanation is the 'Poohsticks phenomenon' – that currents and eddies in blood vessels are similar at different times, such that many emboli released from the internal carotid artery might be expected to reach the same destination, just as many 'Poohsticks' thrown into a stream from the same point on a bridge follow a similar course.

Why does carotid or vertebral dissection cause TIAs and strokes?

This is either by occlusion from the dissecting vessel or, more commonly, by a thrombus forming within the dissected wall throwing off emboli.

Why might a patent foramen ovale lead to stroke?

While stroke is more likely in people with active venous thromboembolism, small clots may form in the circulation in healthy people that would otherwise be filtered and broken down in the pulmonary circulation. Patent foramina ovales are not uncommon, perhaps as common as 10–20% in the adult population, and usually asymptomatic.

How may aortic arch disease or subclavian artery disease cause TIAs or strokes?

Subclavian steal syndrome or phenomenon refers to brainstem ischaemia resulting from diversion of blood flow from a vertebral or basilar artery to a subclavian artery. This is due to occlusive disease of either the subclavian artery or the innominate artery before it branches off at the vertebral. The subclavian artery is fed by retrograde flow from the vertebral artery via the carotids and the circle of Willis. Haemodynamic stability is possible until there is excessive demand in the upper limb. In this situation blood is 'stolen' – diverted – from the cerebral circulation resulting in transient cerebral ischaemia. This may be suspected clinically by the absence of a pulse or by a difference in blood pressure (> 20 mmHg) between the two arms. Vertigo and syncope may result. The condition is demonstrated by computed tomography (CT) angiography. Treatment is by surgical reconstruction or bypass of the subclavian artery.

What are crescendo TIAs?

These are TIAs that rapidly increase in frequency or severity; Royal College of Physicians guidelines define these as more than one TIA in a week. They warrant urgent admission to hospital. They are not very common, and are usually the result of carotid stenosis or a stroke 'mimic' such as a tumour. Urgent brain imaging is needed.

Which patients with a TIA are at highest risk of subsequent stroke?

Two prognostic scores, the ABCD score to predict risk of stroke at 7 days and the California score to predict risk of stroke at 90 days, were validated by a study by Johnston et al for predicting stroke risk after a TIA. The study also showed that a new unified score, ABCD based on five clinical factors, had greater predictive value. The validity of ABCD is also supported by studies identifying age, limb weakness, and diabetes as risk factors for stroke after a TIA. Aspects of ABCD (e.g. unilateral weakness, speech disturbance, prolonged TIA duration) may have prognostic value because they improve the diagnosis of TIA. Features that are important vascular risk factors (increasing age, high blood pressure, and diabetes) are likely to be relevant to the cause of future stroke. The unified ABCD^2 score (range 0–7) is a summation of five independent risk predictors (Table 2.35). The prevalence of stroke is also shown in Table 2.35. Additional risk factors might augment the predictive accuracy of ABCD^2 (e.g. frequent TIAs, symptomatic large artery disease, new ischaemic lesions on imaging).

How should patients with TIAs be managed following risk stratification?

A successful TIA service should offer a rapid TIA/stroke clinic outpatient appointment, 24-hour advice from a stroke specialist, determination by phone if TIA or a mimic (migraine with aura, focal seizure, syncope, mononeuropathy), admission if there are ongoing symptoms of stroke, and availability in the next clinic if a resolved TIA with blood tests, with antiplatelet and statin therapy initiated by the GP.

High risk

People who have had a suspected TIA who are at high risk of stroke (ABCD^2 score ≥ 4) should have:

- Aspirin (300 mg daily) started immediately.
- Specialist assessment and investigation within 24 hours of onset of symptoms with neuroimaging – increasingly diffusion-weighted magnetic resonance imaging (MRI) – and carotid duplex/Doppler ultrasound; specialist assessment includes exclusion of stroke mimics, identification of likely causes, and appropriate investigation and treatment. Referral for carotid endarterectomy in patients with TIA or non-disabling stroke with eligible carotid stenosis should ideally be within 7 days.
- Secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

People with crescendo TIAs (≥ 2 TIAs in a week) should be treated as high risk even though they may have an ABCD^2 ≤ 3. Scoring systems also exclude certain populations that may be at particularly high risk of stroke, such as those with recurrent TIAs and those on anticoagulation treatment, who also need urgent evaluation.

Lower risk

People who have had a suspected TIA who are at lower risk of stroke (ABCD^2 ≤ 3) should have:

- Aspirin (300 mg daily) started immediately
- Specialist assessment and investigation as soon as possible, but definitely within 1 week of onset of symptoms
- Secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

Table 2.35 ABCD^2 risk score and prevalence of stroke (%) at 2, 7 and 90 days after a transient ischaemic attack

ABCD^2 score			
Age (≥ 60 years = 1)			
Blood pressure (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg = 1)			
Clinical features (focal weakness = 2, speech impairment without focal weakness = 1)			
Duration of symptoms (≥ 60 min = 2, 10–59 min = 1)			
Diabetes = 1			
Risk group (score)	**2-day stroke**	**7-day stroke**	**90-day stroke**
Low (0–3)	1.0	1.2	3.1
Moderate (4–5)	4.1	5.9	9.8
High (6–7)	8.1	12	18

Late presentation

People who have had a TIA but who present late (more than 1 week after their last symptom has resolved) should be treated as though they are at lower risk of stroke.

What are the indications for brain imaging in those with a suspected TIA or non-disabling stroke?

While all people with symptoms of acute stroke need urgent brain imaging, there is less evidence to recommend brain imaging where symptoms have completely resolved by the time of assessment. People who have had a suspected TIA (symptoms and signs completely resolved within 24 hours) should be assessed by a specialist before a decision on brain imaging is made. Those who need brain imaging should undergo diffusion-weighted MRI except where contraindicated, in which case CT scanning should be used. Examples where brain imaging is helpful in the management of TIA are: those being considered for carotid endarterectomy where it is uncertain whether the stroke is in the anterior or posterior circulation; those where haemorrhage needs to be excluded, e.g. long duration of symptoms or on anticoagulant therapy; those where an alternative diagnosis (e.g. migraine, epilepsy or tumour) is being considered.

High risk

Those with suspected TIA at high risk of stroke (e.g. $ABCD^2$ score ≥ 4, or crescendo TIA) in whom the vascular territory or pathology is uncertain should undergo urgent (within 24 hours of onset of symptoms) brain imaging, preferably with diffusion-weighted MRI.

Lower risk

Those with suspected TIA at lower risk of stroke (e.g. $ABCD^2 \leq 3$) in whom the vascular territory or pathology is uncertain should undergo brain imaging, preferably diffusion-weighted MRI, within 1 week of onset of symptoms

What are the contraindications to MRI?

These include people who have any of the following: a pacemaker, shrapnel, brain aneurysm clips, metal heart valves, metal fragments in the eyes, or severe claustrophobia. The other problem with MRI is the high rate of 'incidentaloma' identification. Cavernous malformations are very common incidental findings that may produce TIA symptoms or seizures. Tumours (usually benign) occur in 1 : 145 cases, white matter lesions in 1 : 15, micro-bleeds are common and an overall rate of incidental findings is 10%.

What are the indications for carotid imaging in those with a suspected TIA or non-disabling stroke?

All people with suspected TIA or non-disabling stroke who after specialist assessment are considered candidates for carotid endarterectomy (anterior circulation) should have carotid imaging within 1 week of onset of symptoms. People who present more than 1 week after their last symptom of TIA has resolved should be managed using the lower risk pathway.

How should carotid imaging results be interpreted and managed?

Carotid imaging reports should clearly state which criteria – European Carotid Surgery Trialists' Collaborative Group (ECST) or North American Symptomatic Carotid Endarterectomy Trial (NASCET) – were used when measuring the extent of carotid stenosis. People with stable neurological symptoms from TIA or acute non-disabling stroke who have symptomatic carotid stenosis of 70–99% according to the ECST criteria or 50–99% according to the NASCET criteria should:

- Be assessed and referred for carotid endarterectomy within 1 week of onset of stroke or TIA symptoms; the use of carotid early stenting is without sufficient evidence for guideline recommendation
- Undergo surgery within a maximum of 2 weeks of onset of stroke or TIA symptoms – the number needed to treat to prevent one major event is five in the first 2 weeks but 125 after 12 weeks; beyond 4 weeks the risks outweigh benefits
- Receive best medical treatment (antiplatelet agents, blood pressure control, cholesterol lowering through diet and drugs, lifestyle advice).

People with stable neurological symptoms from TIA or acute non-disabling stroke or who have symptomatic carotid stenosis of less than 50% according to the NASCET criteria, or less than 70% according to the ECST criteria, should not undergo surgery but receive best medical treatment. Although the evidence for endarterectomy is for stenosis at a certain threshold, compelling symptoms and severe stenosis that does not reach threshold may still warrant referral to vascular surgeons for consideration, especially if the lesion is friable and/or there are crescendo or recurrent TIAs thought to be the result of that carotid stenosis.

Would you consider referral for consideration of endarterectomy in a patient with asymptomatic carotid stenosis?

This is contentious, with emerging evidence of benefit balanced against a 1–2% risk of a severe stroke due to the procedure itself as atheromatous material is dislodged and endothelium disturbed.

Do carotid stenoses merit treatment with warfarin?

Antiplatelet therapy is the antithrombotic treatment of choice following a TIA, rather than warfarin, together with modification of other risk factors and urgent consideration of endarterectomy.

Would you anticoagulate a patient with recurrent TIAs despite antiplatelet therapy?

This is contentious. Recurrent TIAs should generally still be treated with antiplatelet therapy except where an embolic source has been identified, in which case warfarin is appropriate. In an acute situation, where TIAs are 'hotly' recurring, intravenous heparin may be considered, and is very important in atrial fibrillation or with clinically relevant carotid stenosis, following brain imaging that excludes alternative pathology, and with a plan for urgent or early consideration of carotid endarterectomy in the latter.

How is carotid dissection managed?

It is usually managed with antithrombotic therapy, either anticoagulation or antiplatelet therapy. There is not a strong evidence base to guide.

What secondary prevention measures would you recommend for a patient after a suspected TIA?

The risk of stroke after a TIA is highest in the first year and patients remain at increased risk without secondary prevention. Measures are listed in Table 2.36 and also discussed in more detail in Case 3.27 (Anterior circulation stroke syndromes).

The EXPRESS study, a before and after study and not a randomised controlled trial, showed the marked benefits of faster treatment after TIA or minor stroke.

Table 2.36 Secondary prevention after a suspected transient ischaemic attack (TIA)

Management strategy	Indication
Carotid endarterectomy	Symptomatic carotid stenosis ≥ 70% (ESCT criteria)
Antiplatelet therapy (aspirin and dipyridamole, or clopidogrel)	Ischaemic stroke or TIA
Anticoagulation	Embolic source (atrial fibrillation, mural thrombus)
Antihypertensive therapy	To achieve targets
Statin therapy	To achieve targets
Modification of other CVD risk factors (smoking cessation, increase exercise, meticulous glycaemic control)	All patients

CVD, cardiovascular disease; ESCT, European Carotid Surgery Trialists' Collaborative Group.

Would you consider statin therapy in an 89-year-old following a TIA?

This is treatment 'outside the evidence-based box'. Although caution should be observed in extrapolating data from clinical trials to different patient groups, older people are under-represented in clinical trials and absence of evidence does not equate to absence of benefit and a treatment with evidence so compelling as statin therapy should be considered in an independent, free-living person 'outside the box'.

CASE 2.17 WEAKNESS AND WASTING

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr John Willoughby, aged 68 years

Thank you for admitting this man, who has been losing a dramatic amount of weight over the last 3 months (around 12 kg). He was seen recently in the outpatient clinic where it was noted that he had ataxia and postural hypotension. Normal blood tests included urea and electrolytes and renal function, liver function tests, calcium, C-reactive protein, full blood count, thyroid function and prostate-specific antigen. An urgent computed tomography brain scan was normal, as was a synacthen test, and he was started on fludrocortisone without effect. He has subsequently developed what appears to be a right radial nerve palsy, and possibly ulnar wasting of the hand together with fasciculation. He is due for clinic review soon but his ataxia has worsened considerably and I feel he needs urgent inpatient assessment.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr John Willoughby is a 68-year-old man who has just been admitted to hospital for investigation of weight loss, unsteadiness and light-headedness. His weight loss has been rapid, over 2–3 months. He has no significant past medical history other than rheumatic fever as a child. He takes no medications. He is an ex-builder, and has a past history of alcohol excess (up to 10 units per day but absolutely no alcohol in the past 12 months) and heavy smoking. There is no family history of balance problems. His balance is very unsteady, like being on a ship in rough seas, and he has a tremor of both arms that is worse with movement. He has recently developed weakness of his right hand, and noticed that his muscles are wasting quickly. He lives alone, and is not looking after himself very well, but is a little passive about this.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

The differential diagnosis of subacute weakness and weight loss is wide (Table 2.37).

Patient perspective

Although he is not looking after himself and not eating well, his weight loss should not be attributed to this. Whether or not he is perturbed by his situation, he should be offered full social services, occupational therapy and physiotherapy assessments.

Past medical history

Infective endocarditis in the context of rheumatic heart disease must be considered, but the normal C-reactive protein would be very unusual.

Drug and allergy history

He appears not to be on any anorexogenic drugs.

Family history

A neurodegenerative disorder should always be considered such as a familial spinocerebellar disorder. Motor neurone disease is rarely hereditary.

Social history

Alcohol-induced cerebellar degeneration could account for ataxia, but the profound wasting, focal neurological signs and weight loss should not be attributed to alcohol alone. The heavy smoking history makes a search for cancer paramount.

Discussion

How might malignancy affect the nervous system?

Possible mechanisms are outlined in Box 2.51.

Table 2.37 Causes of subacute weakness and weight loss

Cause	Likelihood
Malignancy, especially paraneoplastic syndrome	High given weight loss, ataxia and smoking history Subacute onset and speed of progression unusual for most conditions, even for motor neurone disease, but typical of a paraneoplastic syndrome
Primary neurodegenerative disease, e.g. motor neurone disease, multiple sclerosis	Possible given wasting and weakness, ataxia and postural hypotension (Creutzfeld-Jacob disease remains rare but must be considered with rapid weight loss and ataxia)
Spinal cord pathology	Low Does not explain lower motor neuron signs unless spinoradicular disease, e.g. T1 given hand findings Does not explain ataxia unless part of spinocerebellar ataxia
Guillain–Barré syndrome	Not typical
Myasthenia gravis	Not typical
Myositis	Low Does not explain ataxia or fasciculation
Autoimmune disease including vasculitis	Unusual with normal C-reactive protein
Infection, e.g. tuberculosis, subacute bacterial endocarditis	Unusual with normal C-reactive protein and neurological signs
Alcohol	Possible given alcohol history and ataxia (B12 deficiency must also be considered)
Toxic, e.g. lead poisoning, botulism	Should not be forgotten

SUMMARY BOX – ASSESSMENT AND PLAN

- He should have an urgent chest X-ray, and will almost certainly need a computed tomography scan of his thorax, abdomen and pelvis and magnetic resonance imaging of his brain and brainstem.
- Electrophysiological tests should be performed for any evidence of anterior horn cell disease.
- In addition to a full screen of blood tests, paraneoplastic antibodies are probably warranted.

What are the characteristic features of paraneoplastic syndromes?

These are rapidly progressive, often fatal within a few months. Standard investigations are normal, although high protein and oligoclonal bands in cerebrospinal fluid suggest an immune rather than degenerative cause.

Table 2.38 Paraneoplastic antibodies

Paraneoplastic antibody	Effects	Cause
Anti-Hu (ANNA-1)	Encephalomyelitis Cerebellar neuropathy Sensory neuropathy due to dorsal root ganglion disease Autonomic neuropathy	Small-cell lung cancer
Anti-Yo (PCA-1)	Cerebellar neuropathy (severe gait ataxia, nystagmus, dysarthria, limb ataxia)	Breast cancer Ovarian cancer
Anti-Ma	Cerebellar involvement Brainstem encephalitis (vertigo, ataxia, abnormal eye movements, long tract signs, cranial nerve signs, life threatening)	Breast, lung or colorectal cancer
Anti-Ma2 (Ta)	Limbic encephalitis (amnesia, confusion, seizures) Brainstem encephalitis	Testicular cancer
Anti-Ri (ANNA-2)	Brainstem encephalitis Opsoclonus–myoclonus	Breast cancer Small-cell lung cancer
Anti-recoverin	Retinopathy	Small-cell lung cancer
Anti-voltage-gated calcium channel	Lambert–Eaton myasthenic syndrome	Small-cell lung cancer
Anti-CV2 (CRMP-5)	Encephalomyelitis, chorea, uveitis, optic neuropathy	Small-cell lung cancer Thymoma
Anti-amphiphysin	Encephalomyelitis Stiff person syndrome (axial muscle stiffness)	Small-cell lung cancer Breast cancer

Box 2.51 **Malignancy and the nervous system**

- Direct invasion
- Spinal metastases
- Opportunistic infection
- Neoplastic meningitis (e.g. cortical signs, headache, cranial neuropathies)
- Radiotherapy – white matter necrosis, Lhermitte's phenomenon (transient), transverse myelitis (spastic paraparesis), localised cord necrosis with oedema
- Metabolic – ectopic hormone production
- Paraneoplastic neurological disorders

What types of paraneoplastic syndrome do you know of?

These are outlined in Table 2.38.

CASE 2.18 MULTIPLE SCLEROSIS

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Dear Doctor

Re: Mr Keith Belham, aged 40 years

Mr Bertram has become very unsteady on his feet in the last few days and now has a markedly ataxic gait. Last year he had an episode of optic neuritis and the ophthalmologist suggested to him, when asked, that multiple sclerosis could be a possibility. I am clearly concerned that this is a second episode of demyelination and appreciate your urgent assessment.

Yours sincerely

Scenario

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Keith Belham is a 40-year-old man who has become very unsteady on his feet in the last few days and now has a markedly lurching gait, rather like being on ship. Last year he had an episode of visual blurring with pain in the right eye and the ophthalmologist suggested to him, when asked, that multiple sclerosis could be a possibility. He took this rather well, and tends to be someone who lives from day to day, taking whatever life brings. He would not describe himself as an alcoholic, but does 'like a drink' and has recently drunk a little more than usual (a bottle of whisky a week) to celebrate passing an Open University degree in Aboriginal culture. He is Australian by birth, and his sister (his only surviving relative) lives in Melbourne. He is hoping to go back to live in Australia soon, and work as a tour guide. He did not know his father. A second sister committed suicide 10 years ago. His mother died at the age of 60 from an unexplained neurodegenerative illness. Apart from the visual symptoms last year and the current symptoms, he has had a number of episodes of tingling in the right arm. He has normal bladder, bowel and erectile function.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Elicit the range of symptoms.** Symptoms in multiple sclerosis (MS) tend to emerge over days, plateau and then resolve slowly. Symptoms characteristically may reappear transiently or worsen with increased body temperature (Uhthoff phenomenon). Symptoms arise from plaques in white matter tracts and so symptoms of cortical dysfunction such as dysphasia, hemiparesis or hemianopia are uncommon. Common symptoms in MS are limb weakness (initial presentation in 40%), optic neuritis (initial presentation in 22%), sensory disturbance (initial presentation in 21%), spasticity, ataxia, diplopia (initial presentation in 12%), fatigue, neuropathic pain, mood disturbance, erectile dysfunction and bladder and bowel dysfunction. Symptoms are more easily evaluated by considering the sites of demyelination in Table 2.39.

■ **Consider the types of MS.** 80–85% of patients present with a relapsing–remitting form of MS and after many years most enter a secondary progressive phase; 15–20% of these have a mild course with minimal disability at 15 years ('benign'); about 15% present with a slowly progressive pattern called primary progressive MS.

■ **Consider differential diagnoses.** The diagnosis is in doubt if the features in Box 2.52 are true. Possible differential diagnoses are listed in Box 2.53.

Patient perspective

His rather passive approach to his symptoms should not detract you from engaging and involving him in your thoughts and recommendations.

Past medical history

He is previously well.

Table 2.39 Sites of demyelination and possible clinical features

Site of demyelination	Possible clinical features
Spinal cord	Limb weakness, e.g. spastic paraparesis Sensory symptoms, e.g. limb numbness, 'cold water' trickling feeling along a limb Lhermitte's phenomenon (neck flexion induces an 'electric shock' sensation running down the back owing to a cervical plaque) Erectile dysfunction Urinary frequency or retention Constipation Spasticity of limbs, with flexor spasms, cramps or spontaneous clonus Pseudoathetosis (loss of sensory feedback from arm due to a cervical plaque causing involuntary writhing movements of fingers and wrist when eyes closed)
Brainstem	Diplopia (including internuclear ophthalmoplegia) Ataxia Vertigo Facial weakness or numbness Dysarthria Dysphagia
Cerebellum	Gait ataxia Limb ataxia Dysarthria
Optic nerve	Optic neuritis (pain, especially on movement, and dimming of vision in one eye, often described as looking through a murky window)
Cerebrum	Mood or memory disturbance

Box 2.52 **Red flags to diagnosis of multiple sclerosis**

- No eye, sensory or sphincter signs in the setting of considerable motor disability
- Lower motor neuron signs (except from disuse)
- Systemic features such as rash or arthropathy

Drug and allergy history

Ask about prescription and non-prescription drugs.

Family history

His family history of suicide should alert you to possible depression. The relative risk of suicide in MS is also increased.

Social history

His social history should focus on his alcohol consumption, home circumstances, support network and travel plans.

Box 2.53 Differential diagnoses of multiple sclerosis

- Structural lesion
- Transverse myelitis (a complete intrinsic spinal cord lesion developing rapidly is compatible with MS but may also be the result of ischaemia or infection)
- Bilateral optic neuropathy to the point of blindness – consider alternative diagnosis, e.g. Leber's hereditary optic atrophy
- Progressive cerebellar syndrome, e.g. metabolic or inherited
- Devic's neuromyelitis (simultaneous optic neuritis and myelopathy of autoimmune origin with normal magnetic resonance imaging which may respond to plasma exchange)
- Relapsing–remitting central nervous system disease in systemic lupus erythematosus
- Neurosarcoidosis (often affects optic nerve and spinal cord)
- Cerebral vasculitis (but usually causes encephalopathy, seizures, headache and fever)
- Leucodystrophies (rare, inherited, demyelinating disorders)

SUMMARY BOX – ASSESSMENT AND PLAN

- This may be an episode of cerebellar demyelination. The possibility of spastic paraparesis due to spinal cord demyelination, however, should also be considered in any patient with possible multiple sclerosis presenting with gait disturbance.
- Reducing his alcohol consumption is less likely to be immediately significant but is important in his overall management.
- He could have an alternative neurodegenerative disorder.
- Investigations should include urgent magnetic resonance imaging.

Discussion

What is MS?

MS is an inflammatory demyelinating disease of the central nervous system (brain, spinal cord, optic nerves) disseminated in time and space. Therefore, either a relapsing–remitting syndrome in one site or a monophasic syndrome in several areas cannot be diagnosed as MS, although a consensus statement allows MS to be diagnosed (McDonald criteria) if there is magnetic resonance imaging (MRI) evidence of new disease activity 3 months or more after one clinical episode. Increasingly the notion of clinically isolated syndromes diagnostic of MS is favoured (e.g. optic neuritis + 'positive' MRI). If the presenting MRI is abnormal, the likelihood of a second clinical attack in the next 14 years increases from 15% to 90%.

What do you know about the epidemiology of MS?

The UK prevalence is 100–150 / 100 000 and incidence around 80 000. It tends to affect the young to middle-aged group. It is twice as common in women. It is more prevalent at greater distances from the equator.

What is the pathogenesis of MS?

It used to be thought MS was an intermittent disease with inflammatory breakdown of myelin, but it is now evident that it is a more continuous pathological process. A genetic predisposition – there are weak associations with human leucocyte antigens (HLA) DR15 and DQ6, and there is a higher prevalence in identical twins and in 20% of patients another family member is affected although a more extensive pedigree raises the possibility of alternative diagnosis – coupled with environmental triggers probably in late childhood lead to autoimmune breakdown of myelin and axonal damage.

The molecular mimicry theory is logical and probable. A T-helper lymphocyte 1 (Th1) pro-inflammatory pathway is probably activated by, say, an environmental antigen such as a microbe. The microbe is presented by an antigen-presenting cell's HLA or major histocompatibility class II peptide to an autoreactive T lymphocyte's T-cell receptor, activating a Th1 lineage. Activated Th1 lymphocytes cross the blood–brain barrier via chemokines and adhesion molecules and encounter neurological tissue with similar molecular pieces to the original antigen causing the Th1 lymphocytes to further propagate the Th1 pathway via interleukin-2 (IL-2) and interferon-γ (IFN-γ), stimulate macrophages via IL-2 and IFN-γ, and stimulate B lymphocytes (Th2 pathways are also involved). Further cytokines such as tumour necrosis factor-α released from macrophages cause damage to myelin, as do demyelinating antibodies from the B-lymphocyte pathway and other mediators such as complement. Combined with these mechanisms is lack of adequate T-suppressor-cell activity.

An acute MS plaque results. The inflammation strips myelin from nerve axons, impairing conduction, but direct axonal damage also occurs from inflammatory mediators such as nitric oxide. Acute attacks of inflammation cause irreversible damage although rapid resolution of symptoms can occur when the inflammation subsides. Secondary atrophic axonal damage from demyelination probably accounts for the secondary progressive phase of MS.

MS is thus a disease of two phases – an initially inflammatory, relapsing–remitting phase when anti-inflammatory drugs might be effective, and a neurodegenerative progressive phase. Remyelination and rearrangement of ion channels on persistently demyelinated axons contribute to recovery.

Is MS one disease or many?

MS may comprise many diseases. Primary inflammatory MS with an autoimmune basis involving Th1 and Th2 pathways with macrophage and antibody destruction of neurons is well established scientifically. But initial myelin destruction (mechanism unknown) with a secondary inflammatory response to 'mop up' myelin fragments may occur in some people.

Do you know of any diagnostic criteria for MS?

The Poser diagnostic criteria since the early 1980s relied on evidence of at least two relapses typical of MS and evidence of involvement of white matter in more than one site in the central nervous system, the concept of 'lesions scattered in time and space'. The more recent McDonald criteria allow earlier diagnosis of MS (Table 2.40) after one clinical attack if MRI criteria are also present, although it has been suggested that MRI inaccuracy may lead to overdiagnosis. A single episode or clinically isolated syndrome involves the spinal cord in 50% of cases, the optic nerve in 25%, the brainstem in 15% and the cerebrum rarely.

Table 2.40 McDonald criteria for multiple sclerosis (MS) diagnosis

Clinical presentation	Additional data needed
≥ 2 attacks (relapses) ≥ 2 objective clinical lesions	None (clinical evidence sufficient, additional evidence desirable but must be consistent with MS)
≥ 2 attacks 1 objective clinical lesion	Dissemination in space demonstrated by: MRI or positive CSF and ≥ 2 MRI lesions consistent with MS or further clinical lesion involving a different site
1 attack ≥ 2 objective clinical lesions	Dissemination in time demonstrated by: MRI or second attack
1 attack 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: MRI or positive CSF and ≥ 2 MRI lesions consistent with MS and Dissemination in time demonstrated by: MRI or second attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF and Dissemination in space demonstrated by: MRI evidence of 9 or more T2 brain lesions or 2 or more spinal cord lesions or 4–8 brain and 1 spinal cord lesion or positive VEP with 4–8 MRI lesions or positive VEP with < 4 brain lesions plus 1 spinal cord and Dissemination in time demonstrated by: MRI Or continued progression over 1 year

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; VEP, visual-evoked potential.

How would you investigate a patient with possible MS?

The importance of MRI is demonstrated in Table 2.40. For every clinical relapse about 10 MRI lesions are seen. Serial MRI therefore demonstrates progression more rapidly than waiting for clinical relapses. In young patients MRI appearances are characteristic, but in older patients white matter high-signal changes are less specific and can be seen in healthy people or associated with cerebral ischaemia.

Unilateral delay in visual-evoked potentials (in which scalp electrodes record potentials generated in the cortex by a pattern-reversing image) is the most sensitive indicator of previous subclinical optic neuritis, and is positive in the vast majority of people with MS.

Oligoclonal bands in cerebrospinal fluid but not serum indicate inflammation confined to the central nervous system and are seen in 95% of clinically definite MS, their absence raising diagnostic doubt, although they are present in other central nervous system inflammatory conditions such as vasculitis and paraneoplastic syndromes.

What symptomatic treatments are used in MS?

These are outlined in Box 2.54.

How are acute relapses treated?

Methylprednisolone 500 mg to 1 g orally or intravenously for 3–5 days is advocated.

Box 2.54 **Symptomatic treatments in multiple sclerosis (MS)**

The most amenable symptoms to treatment are spasticity and urinary dysfunction.

- Spasticity often affects the legs. Baclofen, titrated slowly, is the most widely used treatment, acting on γ-aminobutyric acid receptors to suppress reflex arcs that have been released from higher inhibitory control. Side effects are sedation and weakness. Tizanidine modulates pre-synaptic release of excitatory amino acids. Dantrolene and gabapentin have been used. Cannabinoids bind to cannabinoid receptors throughout the body but especially the central nervous system and help inhibit the overactive nerve impulses that lead to spasticity.
- Bladder problems are generally one or both of storage failure leading to frequency or emptying failure leading to hesitancy and retention. In the former, anticholinergic drugs such as oxybutynin may help; in the latter, confirmed by a post-micturition bladder volume of > 100 ml, intermittent self-catheterisation may be indicated.
- Erectile dysfunction is common in MS, and treated with phosphodiesterase inhibitors.
- Tremor, usually rubral, is difficult to treat.
- Fatigue is difficult to treat.
- Depression is common and should be proactively considered.

What disease-modifying treatments (DMTs) are used in MS?

The standard DMTs are interferon-β (IFN), a cytokine with widespread activity within the immune system available in three preparations – Betaferon (IFN-β1b), Avonex or Rebif (IFN- β1a), or glatirimir acetate (GA), subcutaneously self-injected, generally once to thrice weekly.

Relapsing–remitting MS

Early treatment has been shown to have better outcomes. IFN or GA reduces relapse frequency by about one-third; in the average patient this means a reduction from three to two relapses over 3 years. DMT can also reduce the severity of attacks, the number of new lesions on MRI and progression. The Association of British Neurologists suggests treatment in ambulant patients with at least two relapses in the past 2 years. Treatment may be accompanied by a slowing of the accumulation of disability. Treatment late in disease when no relapses are occurring is of doubtful benefit. Generally, a period of observation to see if the course is likely to be benign is followed by IFN as standard treatment. GA may then be considered if a further one or two relapses occur. Currently it is not possible to predict who will develop more severe MS (possible indicators include age, sex, relapse frequency, relapse severity, degree of recovery and MRI lesion load) and there is no evidence that treating a clinically isolated syndrome reduces relapses.

Primary and secondary progressive MS

Evidence does not support benefit from IFN in primary progressive disease, and limited evidence of benefit in secondary progressive MS is rather outweighed by trials failing to show benefit. Most neurologists do not advocate IFN in progressive disease because it is thought to reflect neurodegeneration rather than inflammation.

Novel potential treatments

MS is a disease of immune dysregulation of T and B cells, and many molecular therapies now offer hope of long-term control by reducing myelin attack by myelin-reactive cells and improving T-lymphocyte suppressor function. These include:

- Rituximab, an anti-CD20 monoclonal antibody used in rheumatoid arthritis and haematological malignancies because of its selective depletion of mature B cells, depleting potentially pathogenic B cells from the population whilst preserving B-cell precursors and plasma cells and so preserving immune competence
- Alemtuzumab (anti-CD52, Campath), used in chronic lymphocytic leukaemia, which selectively depletes mature B and T cells; its long-term suppression of CD4 and CD8 T lymphocytes profoundly reduces autoreactive central nervous system inflammation
- Natalizumab, an inhibitor of an integrin adhesion molecule that attenuates access of immune cells across the blood–brain barrier; progressive multifocal leucoencephalopathy has been a reported side effect
- Daclizumab (anti-CD25), which blocks the IL-2 receptor and increases the CD56 natural killer cell population and restores immune regulation of reactive T cells
- Fumarate, which induces Th2-like cytokines and suppresses harmful Th1-induced inflammatory responses
- Laquinimod, whose mode of action is unclear, but which seems to prevent entry of reactive T lymphocytes into the central nervous system
- Fingolimod (FTY-720), which chemotactically prevents egress of potentially harmful T lymphocytes from lymph nodes without affecting peripheral T-cell function or B-cell function.

What do you know about the course and prognosis of MS?

Initially, most patients experience relapses that resolve completely or partially, usually with one or two relapses per year. At 10 years 50% of patients have secondary progressive MS (90% at 25 years) with continuous accrual of deficit with or without relapses. Primary progressive disease affects about 10% of patients, more commonly men. Disabling paraparesis eventually affects one-third of patients, 25% are incontinent or catheterised and 15% are confined to a wheelchair; 50% of patients are unable to work at 5 years, and after 15 years 50% need at least a stick to walk 100 yards; 10% remain minimally disabled at 10 years ('benign MS').

CASE 2.19 TREMOR

Candidate information

Role

You are a doctor in a care of the elderly clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Robert Matthews, aged 68 years
> Thank you for seeing Mr Matthews, who has a tremor affecting his right arm. He is new to our practice but tells me he has had the tremor for some years but that it is worsening. He has no bradykinesia or rigidity but I am wondering if he might have Parkinson's disease. I would appreciate your advice.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Robert Matthews is a 68-year-old man who has had a tremor affecting his arms for around 5 years. It can affect either arm and is worse on activity but especially so when he is aware of people watching. There has been some difficulty in the past on the part of physicians deciding whether he has essential tremor or Parkinson's disease. He once tried propranolol but it made him feel 'washed out'. He takes atenolol 50 mg for mild hypertension (recent blood pressure 140/80 mmHg). He has recently changed his GP, having moved to a new area. He now has a prominent head tremor and sought a further referral as he would now like to receive some treatment. He does not have any slowness or rigidity, has a very steady gait, and has no reduction in facial expression or blink frequency (he has acquaintances with Parkinson's disease who do). He has noticed an extremely good therapeutic response to quite small doses of alcohol but understandably avoids it as a therapeutic measure except in very special circumstances. He lives with his wife, is retired but chair of the 'Age Concern' organisation locally, and has no other medical history of note. As a further problem, he has noticed a creepy crawly sensation in his legs for the past 2 years that appears to be a separate problem entirely to his other symptoms.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

Types of tremor are listed in Table 2.41.

Patient perspective

Establish his ideas and concerns about the tremor. Reassure him that you agree it does not look like Parkinson's disease. Explore his reactions to propranolol, and his willingness or otherwise to reconsider this drug, assuring him of a more cautious introduction to it. If he is unhappy to reconsider it despite explanation, explain that other strategies are possible. Find out what he hopes to expect from treatment.

Past medical history

Ask about blood pressure readings.

Drug and alcohol history

Ask if he knows what dose of propranolol he was started on.

Family history

There is not infrequently a family history of essential tremor.

Social history

Clearly very important, as essential tremor can have significant social repercussions. The improvement with alcohol is significant.

SUMMARY BOX – ASSESSMENT AND PLAN

- A head tremor is never associated with Parkinson's disease; a jaw tremor is the most one might observe.
- Moreover, he has no other features of Parkinson's disease with a lively facial expression and lots of spontaneous movement and blink frequency.
- He has essential tremor, beyond doubt.
- Only two agents help a significant proportion with essential tremor – propranolol and primidone; all other agents have either not been exhibited to a formal controlled trial or have generally not seen success. The best strategy is to try to get the best out of these agents unless they have unequivocally not been tolerated before.
- Atenolol should be substituted for propranolol. Propranolol is started at 10 mg once daily and if tolerated in 1 week incremented to 10 mg b.d., then 20 mg b.d. a week later and finally 40 mg b.d. Other beta blockers are less effective; propranolol is lipid soluble and crosses the blood–brain barrier. However, some people just feel washed out and less well on propranolol and so it is worth incrementing very slowly to try to improve tolerability.
- If propranolol is not tolerated or ineffective, then primidone may be tried. It is seldom tolerated as a whole tablet and should be started as a quarter tablet (i.e. 62.5 mg) once daily for around 2 weeks then half a tablet for 2 weeks, three-quarters of a tablet and so on.
- For a no-no tremor, botulinum toxin is sometimes effective.
- He may have restless leg syndrome as an additional diagnosis.

Discussion

Are the any tests that can help distinguish the tremor in essential tremor from that in Parkinson's disease?

A radionuclide (DaT) scan can help, and its uses are discussed in Case 3.32 (Parkinson's disease).

What is restless leg syndrome (RLS)?

This is common, affecting 5–15% of the population. There are no involuntary movements but a discomfort due to abnormal sensation (many varieties, e.g. a 'creepy-crawly' feeling) or pain that is relieved by movement. There is a

Table 2.41 Types of tremor

Type of tremor	Causes	Features	Management
Parkinsonian tremor	Parkinson's disease Other extrapyramidal disorders	Rest-predominant tremor, 5 Hz Pill-rolling Asymmetrical Other features of Parkinson's disease	Levodopa Dopamine agonists Enzyme inhibitors
Cerebellar tremor	Cerebellar disease	Action-predominant tremor, 3 Hz	Treat underlying cause
Essential tremor	Family history in 50% Autosomal dominant Identified genes *ETM1* (chromosome 3q13) and *ETM2* (chromosome 2q22–25)	Much more common than Parkinson's disease Postural or action tremor Symmetrical Associated head tremor in 50% Tongue, lips and voice may be affected Anxiety accentuates Alcohol attenuates No other neurological features usual, although cerebellar and cognitive disturbances increasingly seen Slowly progressive but seldom severe	Beta blockers Primidone
Task-specific / performance tremor	e.g. primary writing tremor	Appearance of localised essential tremor but with task specificity of dystonia	Beta blockers Anticholinergics
Orthostatic tremor	Unknown	Affects legs and trunk Only when standing still	Clonazepam
Rubral tremor	Usually seen in multiple sclerosis (lesion in red nucleus, ipsilateral cerebellar dentate nucleus or superior peduncle of midbrain)	Severe tremor Marked worsening with movement	No effective treatment except treatment of underlying disease
Drug-induced tremor	e.g. lithium	Various	Stop drug
Psychogenic	Anxiety	Various	Anxiety management
Physiological	Normal	Small oscillations	None

family history in around 90%, with autosomal dominant inheritance. RLS is more common in females. Four essential criteria must be present for the clinical diagnosis – akathasia, wakeful motor restlessness, rest symptoms relieved by movement, and preponderance towards the end of the day. Secondary causes include pregnancy, iron deficiency, chronic kidney disease, B12 or folate deficiency, hypothyroidism, diabetes, drugs such as steroids and antidepressants, and caffeine, chocolate or alcohol. Investigations should thus include renal function, ferritin, B12 and folate levels, and thyroid function. Iron concentrations may be decreased in the substantia nigra in a significant proportion of patients, the degree of depletion relating to severity, and mirrored by ferritin levels (< 50 usually associated with severe symptoms). There may be postsynaptic dopaminergic dysfunction with abnormal D2 receptor dopamine agonism, this receptor also the iron binder. Treatments include reassurance, avoidance of prolonged sitting, avoidance of precipitants, iron replacement and dopaminergic stimulation. Levodopa tends to cause morning rebound (simply delays onset of symptoms) or evening augmentation of symptoms. Dopamine agonists appear currently most favourable, once in the evening or thrice daily if symptom shifting occurs, but carry the risks of excessive daytime somnolence, obsessive behaviour and gambling. RLS occurs in Parkinson's disease but is not otherwise especially linked to it.

Rheumatological problems

CASE 2.20 BACK PAIN AND OSTEOPOROSIS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Catherine Bingley, aged 62 years

Thank you for seeing this lady who has had back pain for 2 months. There is no history of injury and she is otherwise well. She had a relatively early menopause and I wonder if she might have osteoporosis and might merit a bone densitometry scan.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Catherine Bingley is a 62-year-old woman with a 2-month history of backache. The pain is localised to the mid-thoracic region and is dull, but exacerbated by and sharper on coughing. It sometimes interferes with her sleep. It is not getting worse, but equally is not improving. There is no clear history of trauma or a fall although she did lift heavy garden rubbish about 3 days before the onset of symptoms. She has no joint or muscle symptoms. She has not lost weight and is systemically well. She has been post-menopausal for 20 years and there is a strong family history of early menopause and osteoporosis. There is no other significant family history and in particular no family history of breast cancer. She did not take hormone replacement therapy (HRT) because she had a deep vein thrombosis following childbirth 35 years ago and had been aware that HRT increased the risk of deep vein thrombosis. She has been otherwise previously well. She is divorced and works as a solicitor's secretary. She used to smoke. She is concerned she may have osteoporosis, but has also read in a magazine of a woman with cancer whose initial symptom was back pain.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Determine more about the back pain.** Back pain can be the result of a problem in the back or may be referred from elsewhere such as the genitourinary system. Whereas simple mechanical back pain is very common in young to middle-aged patients with lumbosacral, buttock or thigh symptoms, the 'red flags' in Box 2.55 should be considered.

Box 2.55 **Red flags to back pain**

- Age > 55 years
- 'Non-mechanical' back pain with no clear aggravation by movement or change with posture
- Thoracic pain
- Systemic symptoms such as weight loss or loss of appetite
- Past history of carcinoma (especially colorectal, breast, renal, thyroid)
- Patient with human immunodeficiency virus infection
- Drug history, especially repeat prescriptions for corticosteroids
- Neurological symptoms and signs; any history of bladder or bowel symptoms should also be elicited in determining whether or not back pain is a neurosurgical emergency

Box 2.56 **Main clinical presentations of osteoporosis**

- Overt fracture (wrist, spine, hip), often with low trauma, e.g. fall from standing height or less
- Pain
- Height loss
- Incidental osteopenia noted on X-ray

■ **Consider osteoporosis symptoms.** Osteoporosis is silent until a fracture is sustained. The main clinical presentations are listed in Box 2.56.

Fractures of the wrist or spine occur in younger post-menopausal women, and the hip in older people. A Colles' fracture is often the first sign in women aged 45–65 years. Vertebral fractures may present with severe thoracic back pain, in up to two-thirds without recollection of trauma, but are often asymptomatic. The relative risk of a new vertebral fracture is more than doubled by a previous vertebral fracture and more than quadrupled by a previous vertebral fracture with low bone mineral density (BMD). New fractures tend to occur rapidly after the first – a one in five chance within 12 months. Hip fractures are often the presenting feature of osteoporosis in older people, most well over 70 years, and most are associated with osteoporosis. These may be intertrochanteric, femoral neck or subcapital. Mortality is 20%, 50% have long-term incapacity and 20% enter long-term care.

■ **Consider falls risk.** Both prevention of falls and prevention of osteoporosis are crucial to prevention of osteoporotic fractures.

Patient perspective

Acknowledge her concerns about osteoporosis and explore her concerns about cancer. While malignancy can present with back pain, she has no alarm symptoms for malignancy but does have risk factors – family history, early menopause and smoking – for osteoporosis and may have sustained a compression fracture during heavy lifting.

Box 2.57 Risk factors for osteoporosis and fractures

For many years, guidance on identifying people at high fracture risk was provided by the Royal College of Physicians, based on an opportunistic case-finding strategy in which clinicians were alerted to clinical risk factors (CRFs) associated with fractures prompting measurement of bone mineral density (BMD); treatment was targeted largely at those whose BMD indicated osteoporosis.

It is now apparent that the presence of several risk factors is associated with a fracture risk greater than can be accounted for by BMD alone. This knowledge underpinned development of the World Health Organization's Fracture Risk Assessment (FRAX) tool, which computes age-specific, 10-year probabilities of major osteoporotic fracture (spine, hip, forearm or proximal humerus) in men and women based on their CRFs and BMD measured at the femoral neck. FRAX then designates people at high, intermediate or low risk based on this information.

Risk factors for osteoporosis used in the FRAX tool

These include:

- Age
- Sex
- Low body mass (< 19 kg/m^2)
- Previous fragility fracture, particularly hip, wrist or spine (vertebral deformity/collapse, height loss/kyphosis)
- Parental history of hip fracture
- Ever long-term use of glucocorticoids (any oral dose for at least 3 months)
- Current smoking
- Daily alcohol consumption of three or more units
- Secondary osteoporosis including: rheumatoid arthritis, untreated hypogonadism in men and women, organ transplantation, type 1 diabetes, hyperthyroidism, gastrointestinal disease, chronic liver disease and chronic obstructive pulmonary disease.

Although falls are an important risk factor for fracture they are not used in the FRAX algorithm because the effect of treatment on reducing falls risk is unclear. Other secondary causes of osteoporosis include: rheumatological disease (osteogenesis imperfecta, Marfan's syndrome, Ehlers–Danlos syndrome, homocystinuria); endocrine disease (primary hyperparathyroidism, Cushing's disease, hyperprolactinaemia); malignancy (myeloma, lymphoma, leukaemia, mastocytosis); drugs (heparin, aromatase inhibitors, androgen deprivation therapy, selective serotonin reuptake inhibitors, proton pump inhibitors, thiazolidenediones). Other risk factors for osteoporosis include low dietary calcium, vitamin D deficiency, physical inactivity and high caffeine intake.

The three most important factors independent of BMD are age over 65 years, a previous fragility fracture and a strong family history of fracture.

Past medical history

■ **Explore factors for risk of osteoporosis and fractures.** Risk factors are listed in Box 2.57.

Drug and allergy history

Ask about drug treatments, in particular repeated courses of corticosteroids for conditions such as asthma, chronic obstructive pulmonary disease or inflammatory bowel disease.

Family history

Elicit any family history of osteoporosis.

Social history

Ask about smoking or heavy alcohol ingestion. Ask how she is coping at home.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ She has strong osteoporosis risk factors and may have sustained a thoracic compression fracture.
- ◆ There is nothing other than back pain, which is a very common symptom, to suggest malignancy.
- ◆ A full screen of blood tests including inflammatory markers should be requested, together with a thoracic spine X-ray.
- ◆ She merits a bone densitometry scan.

Discussion

What is the scale of the osteoporosis problem?

It is estimated that around 2 million women in the UK have osteoporosis. After the menopause, the prevalence of osteoporosis increases markedly with age, from approximately 2% at 50 years rising to more than 25% at 80 years. One in two women and one in five men over 50 years will develop an osteoporotic fracture, the lifetime risk of a vertebral fracture one in three, and a hip fracture one in five. The incidence of an osteoporotic fracture increases markedly with age in women after 45 years, mainly forearm fractures up to 65 years, hip fractures then rising exponentially, and in men fragility fractures after 75 years. Post-menopausal women with an initial fracture are at substantially greater risk of subsequent fractures, e.g. a woman with a vertebral fracture has an increased relative risk of 4.4 for a further vertebral fracture, 2.3 for a hip fracture and 1.4 for a wrist fracture. It is estimated that annually there are 180 000 osteoporosis-related symptomatic fractures in England and Wales, 70 000 hip, 25 000 clinical vertebral and 41 000 wrist. There are marked geographic variations, osteoporosis being most common in white and Asian populations.

What do you understand by bone remodelling?

Bone comprises collagen (mostly type 1) and other proteins and minerals (mostly calcium and phosphate) within hydroxyapatite crystals. There are two types – cortical bone (80%) is dense, envelops the marrow cavity and forms Haversian systems or concentric lamellae around a central canal of blood vessels; trabecular bone (20%) is 'spongy', less dense and forms the centre of long bones, flat bones and vertebrae as a meshwork of trabeculae and marrow-filled spaces and is more metabolically active. Bone provides structural support, is a reservoir for mineral exchange and is dynamic, about 10% being remodelled at any time; it is remodelled in multicellular bone-remodelling units (BMUs), beginning with resorption and ending in new bone formation within the cavity.

Bone resorption

Remodelling begins with bone resorption. Osteoclast precursors in blood, derived from the monocyte–macrophage lineage, are attracted to skeletal micro-damage, where they differentiate into mature osteoclasts by activation of their RANK (receptor activator of nuclear factor-κB) receptors by RANK ligands (RANKL) expressed on osteoblasts and other bone cells. The interaction is inhibited by osteoprotegerin (OPG), a 'decoy' molecule that is analogous to RANK and also binds RANKL. RANK and OPG are members of the tumour necrosis factor (TNF) receptor family, and RANKL is part of the TNF family. Other molecules are involved in differentiation of myeloid precursors to osteoclasts and in transducing signals from RANK to nucleus. Osteoclasts contain membrane pumps that release acid, which dissolves hydroxyapatite and allows proteolytic enzymes to degrade bone matrix, one of the important ones being cathepsin K. When resorption is complete, osteoclasts undergo apoptosis, heralding bone formation.

Bone formation

This begins with attraction of osteoblast precursors derived from marrow stroma to the resorption site. Osteoblasts mature in response to transcription factors Cbfa1 and osterix (Osx), which bind to the promoter of osteoblast-specific genes such as osteocalcin, type-1 collagen and alkaline phosphatase. 'Bone morphogenic proteins' are other growth factors thought to contribute to the formation and differentiation of osteoblast precursors. Lipoprotein receptor-related protein 5 is a further key regulator of bone formation acting downstream of Cbfa1 and Osx and stimulates bone formation when activated by the Wnt protein family, effects opposed by a protein called sclerostin produced by osteoclasts which inhibits bone formation. Mature osteoblasts lay down uncalcified matrix (osteoid) on the bone surface, and this calcifies in about 10 days to form mature mineralised bone. Alkaline phosphatase, produced by osteoblasts, promotes mineralisation by degrading pyrophosphate, an inhibitor of mineralisation. During formation, some osteoblasts become trapped in bone matrix and differentiate into osteocytes, the most abundant cells in bone. Osteocytes produce signalling molecules in response to mechanical loading and have a role in sensing mechanical strain.

What regulates bone remodelling?

It is regulated by circulating hormones and local cytokines. Mechanical loading increases formation whereas pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF increase remodelling. Calciotropic hormones such as parathyroid hormone and 1,25-hydroxyvitamin D increase remodelling to maintain plasma calcium homeostasis. Remodelling is increased by thyroid hormone and growth hormone and suppressed by oestrogen, androgens and calcitonin. Many hormones act by modulating the expression of local cytokines, e.g. sex hormone deficiency enhances the expression of IL-1 and IL-6. Ultimately, the final common pathway of regulation by hormones and cytokines appears to be the RANKL–RANK–OPG system.

Table 2.42 Abnormal bone remodelling and disease

Disease	Bone-remodelling problem
Osteoporosis	Excessive resorption, usually associated with post-menopausal sex hormone deficiency, coupled with determinants of peak bone mass attained in earlier life
Paget's disease	Focal areas of excessive bone turnover (when bone is formed rapidly the collagen fibrils are laid down in a disorderly fashion giving rise to 'woven' bone that is weak and susceptible to fracture)
Bone metastases	Focal increases in osteoclast resorption stimulated by osteoclast-activating factors released by tumour cells, e.g. interleukin-1, tumour necrosis factor, parathyroid hormone-related protein
Osteopetrosis	Greatly increased bone maturation due to failure of osteoclast activity, usually a result of one of the many molecular factors crucial to osteoclast activity, causing nerve compression and marrow failure
Inflammatory disease, e.g. rheumatoid arthritis	Pro-inflammatory cytokine excess enhances bone loss

How do problems with bone remodelling lead to disease?

Most bone diseases result from abnormal remodelling (Table 2.42) that compromises its structure and strength and leads to pain, deformity, fractures and abnormal mineral homeostasis.

What is the pathophysiology of osteoporosis?

Bone mineral density (BMD)

Low BMD is one of the key predisposing factors for osteoporotic fractures. Adult BMD is determined by both *acquisition of peak bone mass* during adolescence and the *degree of subsequent bone loss*. These processes are regulated by genetic and environmental factors at the level of BMUs. Each remodelling cycle is balanced – resorption equalling formation – and lasts 90–130 days. Remodelling cycles can become imbalanced, invariably owing to excess resorption, often because of changes in hormones, dietary intake or mechanical loading.

Acquisition of peak bone mass

Acquisition of BMD is most rapid at 12–15 years and peak BMD is attained by 20–25 years. Genetic factors, sex hormone status and dietary calcium are the main regulators of peak BMD. Impaired acquisition of peak BMD is responsible for 60–70% of the variance in BMD at any age.

Bone loss

Hormonal and environmental factors are the strongest determinants of bone loss after the fourth decade in men and women. During the menopause, oestrogen deprivation enhances bone loss, causing around 1% loss per year, but in a small proportion of women a loss of spine BMD up to 5% per year may occur. It is not possible to prospectively identify this group. Although formation accelerates in an attempt to match resorption around the menopause, it does not catch up. Young amenorrhoeic athletes are at greater risk of osteoporosis because of impaired acquisition of peak BMD and accelerated bone loss. In the elderly, there is chronic uncoupling or imbalance of resorption and formation – resorption normal or slightly increased and formation suppressed, normal or only slightly increased – together with oestrogen or androgen deprivation and often calcium and vitamin D deficiency (dietary, and reduced activation of vitamin D) and secondary hyperparathyroidism accounting for bone resorption at least equivalent to menopausal levels.

Fractures

An osteoporotic fracture occurs as a result of major or minor trauma to a bone of reduced quantity and quality. Fractures in virtually all sites in post-menopausal women can be considered osteoporotic excepting facial and compound road traffic accident trauma. Although there is a strong inverse relationship between BMD and fracture risk, other mechanical factors contribute to bone strength and absolute fracture risk and include the rate of turnover, cortical and trabecular thickness and bone shape; trabecular perforation occurs with increased turnover and leads to disproportionate loss of strength for the amount of bone lost. The lower the BMD, the less force is needed to fracture.

How is osteoporosis defined?

The definition is based on the standard deviation of BMD, called a T score, in relation to the young adult normal mean BMD (Table 2.43).

How would you measure BMD?

Dual-energy X-ray absorption (DXA) employs two energy peaks of X-rays that are absorbed to different extents by bone and soft tissue, and BMD is calculated in g/cm^2 using simultaneous equations. The result is compared with two reference ranges – young adults and age-matched adults. Those at risk of osteoporosis may be targeted for DXA scanning. Although osteophytes and aortic calcification may affect reliability, DXA scanning is the most reliable test available for BMD. Quantitative calcaneal or patella ultrasound and quantitative computed tomography of spine, femur or radius are sometimes used to assess BMD.

Table 2.43 T score

T score	Bone disease	Fracture risk
> −1.0	Normal	Low
−1 to −2.5	Osteopenia	Average
< −2.5	Osteoporosis	High
< −2.5 and fracture	Severe osteoporosis	Very high

Table 2.44 Secondary investigations in osteoporosis

Investigation	Reason
Follicle-stimulating hormone	Detects menopause in hysterectomised women with conserved ovaries – osteoporosis risk higher despite ovarian presence
Immunoglobulin electrophoresis	Myeloma
Renal and liver function	Chronic kidney disease / liver disease
Calcium, phosphate, alkaline phosphatase	'Bone profile'
Thyroid function tests	Hyperthyroidism
Testosterone	Male hypogonadism
Full blood picture / biochemistry / coeliac autoantibodies	Malabsorption
Parathyroid hormone	If hypercalcaemia

Are there any other investigations you might consider in osteoporosis?

Over 90% of patients have no secondary cause. Investigations in selected patients, often men, in whom a secondary cause is suspected are listed in Table 2.44.

Do biochemical markers of bone turnover have an investigative place?

Neither markers of formation (e.g. bone alkaline phosphatase, serum osteocalcin) nor markers of resorption are used in clinical practice.

What treatments are there for osteoporosis?

Drug treatments are described in Box 2.58. Smoking and excessive alcohol should be discouraged. Weight-bearing exercise such as walking is beneficial and non-weight-bearing exercise may reduce fracture risk by improving

Box 2.58 **Osteoporosis drug treatments**

Antiresorptive agents

These include bisphosphonates, raloxifene and hormone replacement therapy (HRT) and mostly prevent menopausal and age-related loss. An initial increase in bone mineral density (BMD) caused by catch-up formation is followed by a plateau or, in the case of more potent antiresorptive agents such as alendronate, sustained by smaller increases in BMD caused by secondary mineralisation. Bisphosphonates are used to prevent and treat osteoporosis in post-menopausal females, corticosteroid-induced osteoporosis in males and females and (although without evidence) osteoporosis in males. They unequivocally reduce overall fracture rates. Alendronate and risedronate are more potent than etidronate. Alendronate reduces vertebral and non-vertebral fractures. In the vertebral arm of the Fracture Intervention Trial (FIT) of approximately 2000 women with existing vertebral fracture, daily alendronate for 3 years halved the risk of a new vertebral fracture and reduced the risk of two or more fractures by 90%. The risk of hip and wrist fractures was reduced by around 50%. This was associated with a rise in BMD of 3.2% in the hip and 8% in lumbar spine. Risedronate reduces vertebral and non-vertebral fractures. Two large multicentre trials of risedronate of more than 3600 post-menopausal women with at least one vertebral fracture demonstrated, after 3 years, almost 45% reduction in new vertebral fractures and significant reduction in non-vertebral fractures. No reduction in new hip fractures was shown but there was an increase in spine BMD of 5% and hip BMD of 3%. Anti-fracture efficacy was evident after a year. Reduction in hip fractures was demonstrated in another study of 5445 women aged 70–79 years with osteoporosis of the hip. Bisphosphonates are generally poorly absorbed and need to be taken on an empty stomach with a full glass of water, the patient upright and abstaining from food for 30 minutes; erosive oesophagitis is a side effect. Bisphosphonates are contraindicated in hypocalcaemia, pregnancy and lactation, and should be used with caution in significant renal impairment. They very occasionally cause jaw necrosis, almost exclusively intravenous bisphosphonate therapy in malignancy, and very occasionally unusual fractures. Alendronate and risedronate are taken once weekly, ibandronate monthly orally and 3-monthly by intravenous bolus, and zolendronate annually intravenously.

Raloxifene is a selective oestrogen receptor modulator; it is tissue specific, having both oestrogenic and antioestrogenic effects. It may confer BMD benefit without breast and uterine risk. It increases BMD at the spine and hip in post-menopausal women and reduces the risk of vertebral fractures, but there is no evidence for hip fracture prevention.

HRT is effective for osteoporosis prevention and treatment but is reserved only for menopausal symptoms because it increases the risk of breast cancer, venous thromboembolism and cardiovascular disease.

Dual action treatment – strontium ranelate

Two pivotal studies, Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS), developed the place of strontium in osteoporosis. In SOTI 1649 post-menopausal women with osteoporosis were treated for 3 years leading to a 41% relative risk reduction for vertebral fractures with benefits seen after 1 year. In TROPOS treatment of 5091 post-menopausal women with osteoporosis led to a significant 16% reduction in all non-vertebral fractures after 3 years; for women at high risk of hip fracture there was a 36% risk reduction. Strontium is administered orally, 2 g once daily as a sachet dissolved in water.

Stimulation of bone formation – teriparatide (recombinant human parathyroid hormone (PTH) peptide 1–34)

Continuous exposure to exogenous PTH causes bone resorption. Paradoxically, PTH stimulates bone formation when administered intermittently, increasing BMD, strength and connectivity. This anabolic effect is achieved both by *de novo* formation on resting bone surfaces and by a positive remodelling balance at the bone-remodelling unit. In a randomised controlled trial of 1637 women with osteoporosis, teriparatide 20 or 40 µg daily by subcutaneous injection over a mean treatment period of 18 months resulted in significant increases in BMD in the spine and proximal femur and significant reductions of 65–70% in vertebral fractures and 53–54% in non-vertebral fractures, but without evidence for reduction in hip fractures. The risk of two or more new vertebral fractures was reduced by 77% in the 20 µg group and 86% in the 40 µg group.

Denosumab

This targets the receptor activator of nuclear factor-κB (RANK)/RANK ligand interaction, and may be effective, although the number needed to treat appears high and a track record of evidence is yet needed and there are concerns about jaw osteonecrosis.

Calcium and vitamin D3 supplementation

These should always be used as supplementary therapy, at doses of around 1200 mg calcium (which is anti-resorptive by suppressing PTH) and 800 IU vitamin D3/calcitriol daily, in those at risk such as older patients.

strength and coordination and reducing the risk of falls. Loss of the effect of gravity on the skeleton (e.g. immobilisation) produces dramatic loss of BMD because of uncoupling (resorption increasing dramatically and formation markedly suppressed), the evidence greatest in younger people. Physiotherapy can help at-risk patients in reducing falls and with pain management. Hip protectors may be used in institutionalised people but otherwise there is limited evidence of benefit. Analgesia, kyphoplasty or vertebroplasty, the injection of 'cement', decrease pain and height loss but vertebroplasty may increase the risk of fracture above and below the treated site.

How might you in practice approach the use of BMD measurement and primary and secondary prevention of osteoporosis fragility fractures?

Guidelines by the National Institute for Health and Clinical Excellence (NICE) on secondary prevention in post-menopausal women were first published in 2005, with subsequent revisions including the addition of primary prevention, but these continued to leave gaps (men, primary prevention in post-menopausal women regardless of age, secondary prevention in men and women regardless of age, glucocorticoid-induced osteoporosis, more robust risk stratification and thresholds for BMD measurement) that were filled by the National Osteoporosis Guideline Group (NOGG).

NICE guidelines

Guidance focuses on post-menopausal women and recommends a range of treatments depending upon age, BMD and number of indicators of fragile bones or clinical risk factors for fractures.

Primary prevention (opportunistic)

Alendronate is recommended first-line therapy for primary prevention for women aged ≥ 70 years with at least one clinical risk factor for osteoporosis or indicator of low BMD confirmed to have osteoporosis (defined by NICE as a T-score of < −2.5 on DXA). In women ≥ 75 years with ≥ 2 independent clinical risk factors or indicators of low BMD, a DXA scan may not be required if considered clinically inappropriate or unfeasible. Women under 75 years must have a diagnosis of osteoporosis, and the number of clinical risk factors and indicators of low BMD depends upon the age. Risedronate or etidronate may be used where alendronate is not tolerated or compliance is not possible, and strontium ranelate where alendronate and either risedronate or etidronate are not tolerated or compliance is not possible, but indications in each situation depend upon a combination of T-score, age and number of independent clinical risk factors for fracture.

Secondary prevention

Alendronate is recommended first-line therapy for secondary prevention of osteoporotic fragility fractures in post-menopausal women confirmed to have osteoporosis. Risedronate and etidronate may be used where alendronate is not tolerated or compliance is not possible, and strontium ranelate or raloxifene where alendronate and either risedronate or etidronate are not tolerated or compliance is not possible, but indications in each situation depend upon a combination of T-score, age and number of independent clinical risk factors for fracture. In all cases for women ≥ 75 years a DXA scan may not be required if considered clinically inappropriate or unfeasible. Denosumab may also be considered. Teriparatide may be considered where alendronate and either risedronate or etidronate are not tolerated or compliance is not possible, or with a contraindication to or intolerance of strontium ranelate, or after an unsatisfactory response to treatment with alendronate, risedronate or etidronate, with stringent combinations of age, T scores and clinical risk factors.

For the purposes of NICE guidance:

- Indicators of low BMD are low body mass index (BMI) (defined as less than 22 kg/m^2), medical conditions (such as ankylosing spondylitis, rheumatoid arthritis, Crohn's disease), conditions that result in prolonged immobility, and untreated premature menopause
- Independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis
- Intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance, and intolerance of strontium ranelate, persistent nausea or diarrhoea
- An unsatisfactory response is defined as another fragility fracture despite adhering fully to treatment for 1 year and evidence of a decline in BMD below pre-treatment baseline.

Guidance that BMD scanning may not be required in women aged ≥ 75 who have had a fragility fracture presumes that most women aged ≥ 75 with fragility fractures have osteoporosis. But DXA scans of women aged ≥ 75 with fragility fractures evaluated by the Lothian and Glasgow fracture liaison services in 2007 showed that only half of them had osteoporosis and bisphosphonates do not appear to prevent fractures in patients with osteopenia.

NOGG guidelines

NICE thus imposes differing clinical risk factor number and T-score requisites for a range of differing ages for all drugs other than alendronate, and also restricts what is considered to be a risk factor. This restricts prevention for many at ongoing risk of further fractures. The NOGG essentially translates widely accepted Royal College of Physicians (RCP) guidance into the setting of the World Health Organization's Fracture Risk Assessment (FRAX) and carries forward two important principles from RCP guidelines. Firstly, since there is no universal screening policy for osteoporosis, a case-finding strategy that identifies patients through previous fracture or clinical risk factors as outlined in the FRAX tool (Box 2.57) is recommended. Secondly, in post-menopausal women with a fragility fracture, treatment may be considered without BMD measurement.

A management algorithm used by NOGG starts by assessing 10-year fracture probability on the basis of sex, age, number of clinical risk factors and BMI (used as a surrogate for BMD). This first set of charts categorises people into high, intermediate or low risk of a major osteoporotic fracture (red, orange or green). What is considered high risk differs for different ages and the intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and therefore rises with age; for example, the guideline suggests treating a 50-year-old with a fracture risk of 7.5%, but sets the treatment threshold at 30% for an 80-year-old; this avoids unnecessarily treating an active 80-year-old and not treating a fragile 50-year-old. Furthermore, since a previous fragility fracture is considered a clinical risk factor by NOGG and contributes to the risk calculation, whilst it is likely that a person with a fragility fracture will qualify for treatment, this is not inevitable. The FRAX score and NOGG guideline does not therefore discriminate cleanly between primary and secondary prevention, but rather makes the following intervention suggestions:

- *Red (high risk):* these women and men should be considered for treatment without BMD testing.
- *Orange (intermediate risk):* these women and men should have BMD testing and their probability recomputed with the result; a second set of charts for this purpose shows 10-year fracture probability on the basis of sex, age, number of clinical risk factors and BMD (BMD at femoral neck substituted for BMI); where probability exceeds one or other of the intervention thresholds treatment is recommended and where below further assessment is recommended in 5 years.
- *Green (low risk):* these women and men may be reassured with reassessment in 5 years depending upon the context.
- *Women and men with a previous fragility fracture (secondary prevention):* all women should be considered for treatment without BMD measurement although BMD measurement may be desirable in some younger women. The diminished emphasis on BMD measurement reflects modern consensus that other factors independently contribute to fracture risk. All men should have BMD measurement because of the high incidence of underlying secondary causes of osteoporosis in men.

The guidelines, like NICE, recommend alendronate as first-line therapy but are less restrictive on second-line treatment, which may include other bisphosphonates (including risedronate, ibandronate or zolendronate), strontium, raloxifene or PTH; the guidelines do caution that the high cost of PTH should restrict its use to those at very high risk, particularly of vertebral fractures.

Is monitoring of BMD during treatment sensible?

Treatment aims to reduce the rate of fractures, but if DXA cannot detect a significant change in BMD within a time scale that enables effective changes in management or if the change in BMD does not predict a reduction in fractures after treatment, then monitoring BMD does not appear sensible. Although nearly all women gain BMD with treatment, the large variability associated with the measurement of BMD obscures true treatment response in an individual. Further, only a small proportion of reduction in fractures attributable to treatment is explained by a change in BMD.

When does glucocorticoid-induced osteoporosis begin?

Glucocorticoids simultaneously suppress bone formation and increase resorption, and do so rapidly, within the first few months. Even small oral doses (< 7.5 mg prednisolone) cause some bone loss. Risk increases rapidly in the first 3–6 months and so bone protection should start as soon as long-term corticosteroids are started.

CASE 2.21 JOINT PAIN

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Elaine Tilney, aged 52 years
>
> Mrs Tilney has been complaining of worsening polyarthralgia in her hands and wrists for 6 months. Her blood results are as follows: full blood count normal except for a borderline normochromic–normocytic anaemia; creatinine of 135 mmol / l, otherwise urea, electroytes and liver function tests normal; rheumatoid factor positive. I would be grateful for your further assessment.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Elaine Tilney is a 52-year-old woman who has had increasing pain in the joints of her hands for 6 months. The joints, especially the metacarpals (knuckles), also tend to become spongy and to swell. Pain, and in particular stiffness, is worse in the mornings and starts to subside after an hour or so. Before this started she an episode of swelling in her right knee which lasted around 3 days. She has been increasingly fatigued over the last 6 months, and has taken many days off work. She works as a part-time secretary at the hospital. She lives with her husband and two 'grown up' children in a small house, which she had been trying to improve before putting on the market for sale. However, she has increasingly had to stop work on the house, decorating and so forth, as her hands are too painful to use. Her husband works full time as a nurse on night shifts, and there are tensions at home. She feels he is seldom around, and is always too tired because of his 'full-time job' to decorate or do the housework. Mrs Tilney feels she is trying to cope with her part-time job, home improvement, demanding children who should be out to work and a husband seldom there, against a backdrop of increasing pain and fatigue, and financial worries. If she does not work they will have to sell the house sooner rather than later.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

■ **Determine if symptoms are localised to joints and the pattern and features of joint involvement.** Ask if pain is localised to joints, and not diffuse. The latter could imply a chronic pain syndrome such as fibromylagia. Myalgic symptoms can occur in rheumatoid arthritis. Determine as precisely as you can which joints are affected. Determine if there is joint stiffness as well as pain. Morning stiffness, improving with exercise, characterises an inflammatory arthropathy. Mechanical pain is usually relieved by rest. It is essential to know if there is joint swelling (polyarthritis) as well as pain (polyarthralgia) and stiffness. Any soft-tissue swelling is highly suggestive of inflammatory joint disease.

■ **Consider the differential diagnoses.** The next step is to test each differential diagnosis in turn by asking about symptoms from the diagnostic criteria. In this woman, you should consider rheumatoid arthritis (rheumatoid factor is positive) and systemic lupus erythematosus (SLE) (given the raised creatinine) first. The normochromic–normocytic anaemia supports an inflammatory condition but does not help diagnostically. For rheumatoid arthritis, ask about morning stiffness of > 1 hour, hand joint involvement, symmetrical involvement and nodules. For SLE, ask about rashes, sunlight sensitivity, mouth ulcers and Raynaud's phenomenon.

Patient perspective

Clearly very relevant here is her fatigue, contributed to largely by active inflammatory disease but compounded by her stress and lifestyle. To her, what is going on at home and the impact her symptoms have had on her work are probably more significant than the symptoms themselves. Explore the huge impact her symptoms have had, and try to reassure her that you will try to confirm the diagnosis quickly and get her condition under good control with treatment, reducing symptoms and thereby hopefully improving everything else.

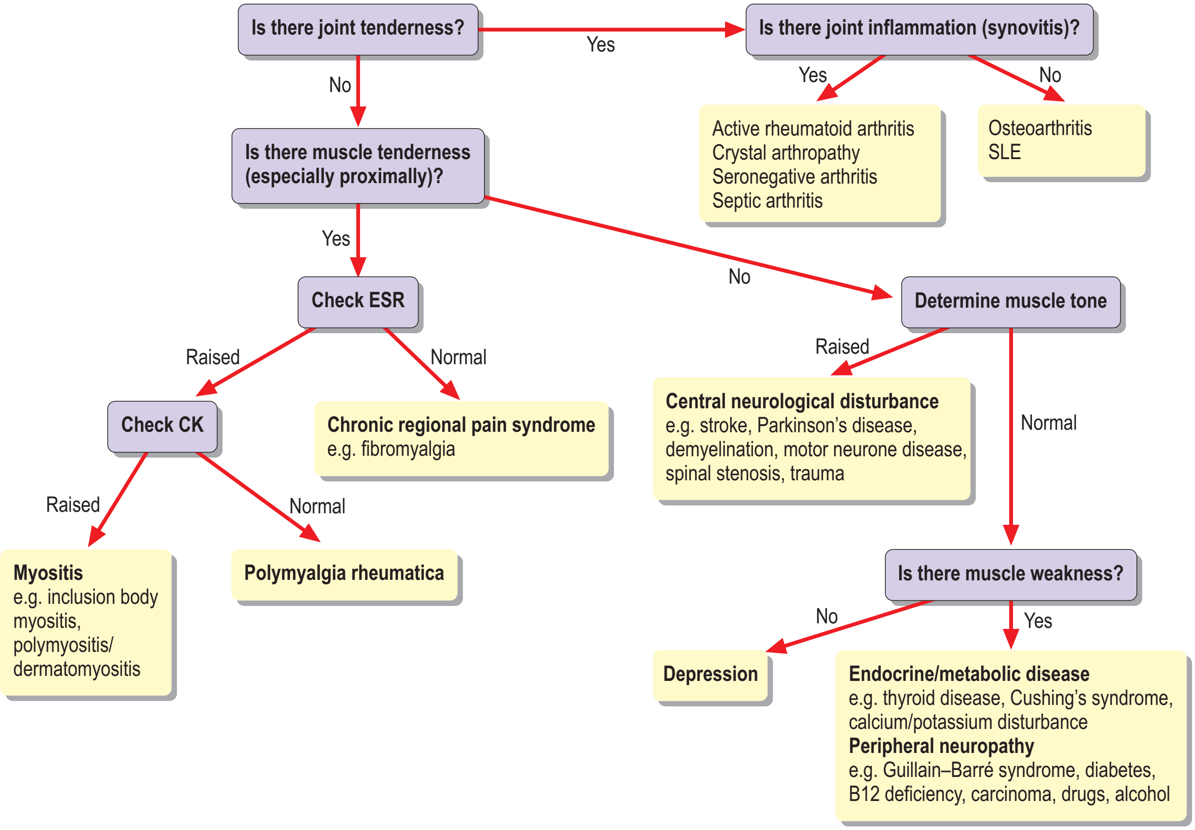

Is there joint tenderness?
Yes
No
Is there joint inflammation (synovitis)?
Yes
No
Active rheumatoid arthritis
Crystal arthropathy
Seronegative arthritis
Septic arthritis
Osteoarthritis
SLE
Is there muscle tenderness (especially proximally)?
Yes
No
Check ESR
Raised
Normal
Check CK
Chronic regional pain syndrome
e.g. fibromyalgia
Raised
Normal
Myositis
e.g. inclusion body myositis, polymyositis/ dermatomyositis
Polymyalgia rheumatica
Determine muscle tone
Raised
Normal
Central neurological disturbance
e.g. stroke, Parkinson's disease, demyelination, motor neurone disease, spinal stenosis, trauma
Is there muscle weakness?
No
Yes
Depression
Endocrine/metabolic disease
e.g. thyroid disease, Cushing's syndrome, calcium/potassium disturbance
Peripheral neuropathy
e.g. Guillain–Barré syndrome, diabetes, B12 deficiency, carcinoma, drugs, alcohol

Figure 2.8 Approach to the differential diagnosis of an older person with decreased mobility and painful joints or muscles. CK, creatine kinase; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus.

Past medical history

She is previously well.

Drug and allergy history

Ask about prescription and non-prescription medications.

Family history

Seek a family history of any autoimmune disease.

Social history

Explore her duties at home with her family and her work in detail.

SUMMARY BOX – ASSESSMENT AND PLAN

- This is very likely rheumatoid arthritis.
- She should be considered for early disease-modifying anti-rheumatic drug treatment and referred to a rheumatologist.

Discussion

Patients, especially older patients, often present with non-specific aches and decreased mobility. Do you have an approach to the differential diagnosis?

An approach to the differential diagnosis of an older person with decreased mobility and painful joints or muscles is given in Figure 2.8.

What do you know about septic arthritis?

Septic arthritis is extremely serious. It is often caused by entry of *Staphyloccocus* from a breach in the skin, or sometimes from another source such as discitis, or sometimes from urine. Organisms tend to seed to damaged joints, as in rheumatoid arthritis, just as they may seed to damaged heart valves causing endocarditis. Multiple joints may be affected, and meticillin-resistant *Staphylococcus aureus* septic arthritis has a very high mortality.

Endocrine problems

CASE 2.22 TYPE 1 DIABETES MELLITUS

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Ms Jill Masters, aged 19 years
>
> Thank you for admitting Ms Masters, who has been complaining of increasing thirst and polyuria over the last few weeks. Her blood glucose monitor reading is 28 and her urine is positive for ketones, although she is relatively well in herself. I have told her that I suspect she has diabetes and am grateful for your ongoing management.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Ms Jill Masters is a 19-year-old medical student in her first year at medical school. She has been increasingly thirsty over the last 4 weeks, and passing larger volumes of urine, and her GP has just admitted her with a new diagnosis of diabetes. She has no past medical history of note and does not take any medications. She is usually very active, leading the university swimming team. Her mother has hypothyroidism but otherwise there is no clear family history of autoimmune disease.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Initial priorities in assessing a patient with newly diagnosed diabetes.** A decision as to whether immediate rehydration and insulin are needed should be made, determined by the presence of dehydration, vomiting or ketonuria. Thirst, polyuria and initial glucose levels correlate less well with the need for immediate insulin.

■ **Presentation of type 1 diabetes.** Presentation varies according to the rate and degree of beta cell failure. The classic presentation is outlined in Box 2.59.

■ **Consider if admission to hospital is warranted.** Admission can be a very negative first experience of newly

Box 2.59 **Presentations of type 1 diabetes**

Classic presentation in childhood/adolescence (peak incidence age 10–14 years)

The patient is usually lean, with acute onset of osmotic symptoms (polyuria when renal threshold of plasma glucose 10 mmol/l reached, polydipsia, weight loss) and ketosis-prone. High levels of islet autoantibodies are present with a high prevalence of susceptibility genotypes (HLA DR3, DR4, DQ2, DQ8).

Adult-onset type 1 diabetes

This is increasingly recognised, with a more indolent presentation, a lower incidence of osmotic symptoms and ketoacidosis and a lower prevalence of autoantibodies and genetic susceptibility.

Latent autoimmune diabetes of adulthood

This is a term for patients aged ≥ 25 years with type 1 diabetes often masquerading as type 2 diabetes with initial control obtained by diet or oral hypoglycaemic drugs; patients have lower levels of C-peptide and are often positive for glutamic acid decarboxylase antibodies.

Older people

Older people can present with type 1 diabetes, often with weight loss and diarrhoea.

Box 2.60 **Indications for admission in newly diagnosed type 1 diabetes**

- Acutely unwell
- Blood glucose > 30 mmol/l
- Ketones in blood
- Moderate to large ketones in urine
- Dehydration
- Vomiting

diagnosed diabetes. Patients invariably proceed to insulin but this can be instituted in a diabetes clinic if there are no features to suggest that insulin is urgently needed and patients are not acutely unwell. Indications for admission are listed in Box 2.60.

Patient perspective

She may initially be very afraid of a diagnosis that has important implications for lifestyle adjustment and carries long-term complications. Some of the skills for breaking bad news may be important, and it is important to emphasise the advances in monitoring and treatment that are less intrusive on lifestyle.

Past medical history

A new diagnosis in this age group is usually type 1 diabetes.

Drug and allergy history

Although certain drugs such as corticosteroids exacerbate hyperglycaemia, drug causes of diabetes are very rare.

Family history

A family history of autoimmune disease is common.

Social history

As well as asking about smoking (future cardiovascular disease risk) and alcohol (which can affect glycaemic control), enquire about university social life and sports activities.

SUMMARY BOX – ASSESSMENT AND PLAN

- She almost certainly has type 1 diabetes and will need expert advice on lifestyle and insulin management by the specialist diabetes team, ongoing follow-up and possible psychosocial support.
- The case may lead to an initial discussion with the examiners about management of diabetic ketoacidosis.

Discussion

What is diabetes?

Diabetes is not a single disorder but a range of autoimmune, metabolic and genetic disorders associated with hyperglycaemia in which defects in insulin secretion or action cause premature atherosclerosis with microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischaemic heart disease, stroke, peripheral vascular disease) complications.

How is diabetes defined?

The prevalence of diabetes has been rising in the last few decades, fuelled by the global rise in the prevalence of obesity. The classification and diagnosis of diabetes are complex and have been the subjects of much consultation, debate and revision over the decades. Expert committees from the World Health Organization (WHO) and American Diabetes Association have varied in their position on the diagnostic criteria for diabetes, based on the measurement of fasting or 2-hour post-load glucose, and more recently there has been debate on whether glycated haemoglobin (HbA_{1c}) should be used. Diagnostic definitions of diabetes mellitus, impaired fasting glucose and impaired glucose tolerance by the WHO are given in Table 2.45.

How is diabetes classified?

The aetiological classification of diabetes has now been widely accepted. Type 1 diabetes and type 2 diabetes are the two main types, type 2 diabetes accounting for the majority (> 85%) of total diabetes prevalence, together with a range of rarer disorders (Table 2.46).

What do you know about maturity onset diabetes of the young (MODY) and how to recognise when other types of diabetes than types 1 or 2 may be the present?

MODY comprises a heterogeneous group of monogenic disorders characterised by beta cell dysfunction. It is

Table 2.45 Diagnosis of diabetes mellitus, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)

	Fasting plasma glucose	**Random plasma glucose**	**Oral glucose tolerance test**
	The preferred test of the three Fasting = no calories for at least 8 hours; water is allowed	**Plasma glucose at any time**	**75 mg anhydrous glucose load dissolved in water with plasma glucose 2 hours later**
Diabetes	≥ 7.0 mmol / l plus symptoms (polyuria, polydipsia, weight loss) (American Diabetes Association recommends HbA_{1c} > 6.5%)	≥ 11.1 mmol / l plus symptoms	≥ 11.1 mmol / l
Impaired glucose regulation ('pre-diabetes' or dysglycaemia)	IFG = ≥ 6.1 and < 7.0 mmol / l (American Diabetes Association recommends ≥ 5.6 mmol /l)		IGT = ≥ 7.8 and < 11.1 mmol / l
Normal	≤ 6.0 mmol / l		< 7.8 mmol / l

In the absence of unequivocal hyperglycaemia with acute metabolic decompensation or symptoms, one of the three tests should be repeated on a different day to confirm diagnosis. HbA_{1c}, glycated haemoglobin.

estimated to cause 1–2% of cases of diabetes. It is important to distinguish MODY from type 1 and type 2 diabetes because optimal treatments are different. Furthermore, first-degree relatives have a 50% probability of inheriting the same mutation, with a greater than 95% lifetime risk of developing diabetes.

Genetic mutations

Mutations in the genes encoding the enzyme glucokinase (GCK) and the nuclear transcription factors hepatocyte nuclear factor 1α (HNF1A) and hepatocyte nuclear factor 4α (HNF4A) are the most common causes of MODY, and in the UK represent 32%, 52%, and 10% of MODY cases, respectively. The prevalence of MODY subtypes differs across countries, with GCK mutations more commonly diagnosed in countries where glucose testing of asymptomatic people is routine. Mutations in at least 10 different genes have been associated with a MODY phenotype.

Clinical features

Features to consider when assessing the cause of diabetes are listed in Box 2.61.

Patients with MODY typically display one or more of:

- A strong family history of diabetes (of any type)
- Onset of diabetes in the second to fifth decade
- Insulin independence (insulin may be needed for optimal control)
- Absence of features of insulin resistance
- Absence of beta cell autoimmunity.

The specific genetic subtype determines the clinical features, prognosis, and treatment response. Table 2.47 summarises similarities and differences between common MODY subtypes and type 1 and type 2 diabetes.

Diagnosis

Diagnostic genetic testing for MODY, by direct sequencing of the genes, is widely available, but largely opportunistic. Guidelines recommend genetic testing for people who match specific clinical criteria: diabetes presenting before the age of 25 years, a strong family history of diabetes, and evidence of insulin independence.

■ **Patients diagnosed with type 1 diabetes who should be referred for genetic testing.** Patients with MODY who present at a young age may be misdiagnosed as having type 1 diabetes and inappropriately treated with insulin. In type 1 diabetes, autoimmune destruction of the beta cells results in complete insulin deficiency within 3–5 years of diagnosis (the 'honeymoon period'), whereas some beta cell function is maintained in MODY. Permanent need for insulin within 3 months of diagnosis, diabetic ketoacidois or positivity for beta cell autoantibodies (ICA, GAD) or C-peptide level ≤ 0.2 nmol/l outside the honeymoon period in a person ≤ 45 years makes type 1 diabetes very likely. MODY should be considered in patients with evidence of continued endogenous insulin secretion, e.g. low insulin dose – < 0.5 units/kg/day, no tendency to ketoacidosis when insulin is omitted, and persistent C-peptide production of > 0.2 nmol/l outside the honeymoon period. C-peptide is less useful for distinguishing MODY from type 1 diabetes close to diagnosis, when endogenous insulin production is still present. MODY is not usually associated with pancreatic autoantibodies. Parental history of diabetes is more common in MODY than in type 1 diabetes, although family history does not discriminate well between the two.

■ **Patients diagnosed with type 2 diabetes who should be referred for genetic testing.** Beta cell dysfunction in MODY typically occurs in the absence of insulin resistance. Patients with young onset (< 45 years)

Table 2.46 Types of diabetes

	Cause	Types	Features
Type 1 diabetes	Autoimmune destruction of insulin-producing beta cells in the pancreatic islets of Langerhans leading to insulin deficiency Complex interaction between genetic susceptibility and environmental factors – possibly susceptible human leucocyte antigen molecules fail to react with pancreatic self-peptides leading to failed deletion of autoreactive T cells and T-cell-mediated autoimmunity against beta-cell antigens promoting autoimmune beta-cell failure; an alternative accelerator hypothesis is that autoimmunity occurs against upregulated beta cells attempting to respond to insulin resistance Associated circulating autoantibodies to beta-cell antigens: islet cell antibodies (ICA) the most sensitive markers of future risk of type 1 diabetes; autoantibodies to glutamic acid decarboxylase (GAD) constitute a major part of ICA, and others are insulin autoantibodies (IAAs) and autoantibodies to the phosphatase IA-2 molecule; most patients have multiple antibodies (≥ 3 predicts a 70–100% chance of developing diabetes within 5–8 years) and often relatives have autoantibodies	Classic presentation in childhood/adolescence Adult onset Latent autoimmune diabetes of adulthood Older people	Classic presentation acute onset of symptom triad of weight loss, polyuria and polydipsia (and risk of ketoacidosis) caused by rapid beta-cell failure and metabolic consequences of insulin deficiency Long pre-clinical prodrome before frank beta-cell failure Clinical presentation in adults often less acute
Type 2 diabetes	Complex metabolic disorder with beta-cell dysfunction (absence of autoimmune destruction) and insulin resistance Genetic basis not fully understood	Metabolic syndrome	Metabolic syndrome associated with reduced life expectancy from widespread vascular complications
Other types	Genetic defects in beta-cell function	Maturity onset diabetes of the young Mitochondrial DNA disorders	
	Genetic defects in insulin action		
	Exocrine pancreatic disorders	Pancreatitis, pancreatic carcinoma, haemochromatosis, drug or chemical induced, infection	
	Endocrinopathies	Cushing's syndrome, acromegaly, glucagonoma, phaeochromocytoma, aldosteronoma, hyperthyroidism, somatostatinoma	
Gestational diabetes	Lack of uniformity on classification, diagnosis and treatment		Increased risk of adverse perinatal outcome

apparent type 2 diabetes, without features of insulin resistance, may have MODY. Clinical features such as acanthosis nigricans, central obesity, hypertension, and dyslipidaemia can be used as surrogate markers of insulin resistance in practice. A family history of diabetes is common in people with young onset type 2 diabetes and does not discriminate well between type 2 diabetes and MODY. Marked sensitivity to sulphonylureas with hypoglycaemia on low or normal doses of sulphonylureas is common with the HNF1A or HNF4A mutation.

Treatment

The mild increase in HbA_{1c} generally seen in GCK-MODY suggests that drugs do not improve glycaemic control in GCK-MODY and insulin and oral hypoglycaemic agents can usually be stopped in patients with GCK-MODY. Sulphonylureas are the optimal treatment in HNF1A/HNF4A-MODY, but patients are very sensitive to them.

What is diabetic ketoacidosis (DKA) and how is it treated?

DKA is defined as metabolic acidosis with a plasma bicarbonate of < 15 mmol/l and a total ketone body concentration of > 5 mmol/l, but in practice it is identified by dehydration, hyperglycaemia, acidosis and ketonuria. It is caused by insulin deficiency in the presence of elevated catabolic hormone levels (catecholamines, glucagon, cortisol, growth hormone) and usually occurs in type 1

Box 2.61 **Features to consider when assessing the cause of young onset diabetes**

History

- Duration and severity of symptoms
- History of obesity, hypertension, or dyslipidaemia (metabolic syndrome)
- History of pancreatic disease
- Family history of diabetes, and age of diagnosis and treatment
- Family or personal history of early-onset deafness (mitochondrial diabetes) and renal cystic disease (HNF1B mutations)
- Personal history or family history of neonatal diabetes or hypoglycaemia

Clinical features

- Signs of insulin resistance, e.g. acanthosis nigricans, abnormal fat distribution (lipodystrophy), central obesity, dyslipidaemia
- Signs suggesting other endocrine disorders, e.g. Cushing's disease, acromegaly

Investigations

- Measurement of autoantibodies to beta cells (islet cell antibodies and glutamic acid decarboxylase)
- Measurement of C-peptide in blood or urine (the cleavage product remaining after insulin has split from its precursor, pro-insulin, with no biological activity, and a measure of endogenous insulin secretion)
- Biomarkers for specific types of maturity onset diabetes of the young
- Genetic testing

Table 2.47 Clinical and biochemical features associated with type 1 diabetes, type 2 diabetes, and the common subtypes of maturity onset diabetes of the young (MODY)

	Type 1 diabetes	Type 2 diabetes	GCK-MODY (30–70% of MODY)	HNF1A (30–70% of MODY)/ HNF4A-MODY (5–10% of MODY)
Typical age of diagnosis (years)	10–30	> 25	Present from birth; presents at any age	15–45
Parental history of diabetes	< 15%	> 50% in young onset type 2 diabetes	One parent usually has impaired fasting glycaemia if tested	60–90%
Obesity / other distinguishing clinical features	Uncommon	Common	Uncommon Mild fasting hyperglycaemia (5.5–8 mmol / l) throughout life; small glucose rise after carbohydrate load	Uncommon Low / normal renal threshold for glycosuria; normoglycaemic in childhood but progressive defect of insulin secretion, diabetes usually diagnosed in the second to fifth decades; marked sensitivity to sulphonylureas
Insulin dependent	Yes	No	No	No
Insulin resistance	Uncommon	Common	Uncommon	Uncommon
Presence of beta-cell autoantibodies	> 90%	Negative	Rare	Rare
C-peptide concentrations	Undetectable / low	Normal / high	Normal	Normal
Diabetic ketoacidosis	Common	Rare	Rare	Rare
Optimal first-line treatment	Insulin	Metformin	None	Sulphonylurea

GCK, glucokinase; HNF1A / 4A, hepatocyte nuclear factor-1α / 4α.

diabetes but can occur in type 2 diabetes. There may be precipitating causes such as infection or myocardial infarction, all having the common denominator of insulin (anabolic hormone) deficiency and catabolic hormone excess promoting the problems in Table 2.48.

DKA is a life-threatening condition requiring immediate hospitalisation and treatment. The aims of treatment are to rehydrate and give insulin. Potassium supplementation is invariably necessary and careful monitoring is necessary. Referral to the critical care team while resuscitating may be appropriate if there is dehydration > 10%, coma, a pH < 7.1 or a plasma sodium < 120 mmol / l or > 160 mmol / l. Fluid resuscitation is with isotonic saline at a rate exceeding losses (e.g. 1 litre first hour, 1 litre next 2 hours, 1 litre next 4 hours, 1 litre 6-hourly) switched to 5% dextrose (and insulin dose halved) when glucose is < 15 mmol / l.

Table 2.48 Diabetic ketoacidosis (DKA)

Hormone problem	Resulting pathophysiology	Biochemical problem	Symptoms
Insulin deficiency	Hepatic glucose mobilisation (e.g. gluconeogenesis) in attempt to compensate for perceived glucose deficiency Decreased peripheral glucose storage (glucose cannot be taken up by cells peripherally)	Hyperglcaemia	Polyuria Polydipsia Dehydration Confusion Drowsiness Coma
Catabolic hormone excess (often due to precipitating cause)	Triglyceride breakdown in adipose tissue resulting in fatty acids which are used to produce ketone bodies (acetone, acetoacetate and 3-hydroxybutyrate) in the ketotic pathway as an alternative source of fuel. The mechanism is the same as that seen in prolonged starvation (Case 4.34) but in starvation insulin levels fall in response to carbohydrate deficiency and alternative energy pathways are sought; in DKA insulin levels are low owing to pancreatic insufficiency and although this results in hyperglycaemia, without insulin glucose cannot be incorporated into cells and is unavailable for energy production mandating a switch to the ketotic pathway as an alternative source of fuel Protein catabolism in muscle	Ketoacidosis	Vomiting Ketonuria Abdominal pain Kussmaul breathing 'Pear drop' or 'nail varnish' or acetone breath due to ketone body metabolism in lungs

It is possible that faster rates are associated with an increased risk of cerebral oedema and slower rates of correction of bicarbonate. When acidosis persists it is probably best to maintain the same dose of insulin and prevent hypoglycaemia with 10% glucose infusion. Insulin may be delivered as 50 units short-acting insulin in 50 ml saline via syringe pump on a sliding scale according to blood glucose (e.g. < 4.0 mmol/l – 0 insulin units/h, 4.1–6.0 – 1 insulin unit/h, 6.1–12.0 – 3 insulin units/h, 12.1–17.0 – 5 insulin units/h, > 17.1 – 8 insulin units/h). The sliding scale may be stopped when there is no ketonuria, acidosis or dehydration and the patient is eating and drinking, ideally having continued to receive their basal insulin if it is pre-existing diabetes. It is possible that rates of fall in plasma glucose > 5 mmol/h may increase the risk of cerebral oedema. A suitable potassium replacement is 40 mmol KCl/l if < 3.5 mmol/l, 20 mmol KCl/l if 3.5–5.5 mmol/l. Complications occur including vomiting with aspiration, thrombotic events, and cerebral oedema.

How is type 1 diabetes managed?

Treatment involves the administration of exogenous insulin to avoid diabetic ketoacidosis, maintaining glycaemic control and preventing the long-term complications. Insulin therapy (Box 2.62) presents a challenge to both patient and health-care professional and a collaborative approach encouraging 'self-management' is necessary. Insulin preparations with differing pharmacokinetic profiles have provided greater flexibility in the management of type 1 diabetes and technological advances in continuous glucose monitoring and continuous subcutaneous insulin infusion via insulin pumps show promise in helping to achieve treatment goals. Other potential therapies include amylin analogues, pancreatic transplantation and islet transplantation, the last a potential modality for possible future delivery of 'engineered' beta cells from human stem cells. The use of immunotherapy for prevention of type 1 diabetes has been disappointing.

What are the principles of nutrition in diabetes?

The old-fashioned approach was a diet low in carbohydrate and high in fat. The modern trend is lower fat and higher carbohydrate, with the concept of knowing the carbohydrate content of foods and responding to carbohydrate units and adjusting insulin accordingly rather than limiting eating.

Does glycaemic control in type 1 diabetes reduce vascular complications?

The Diabetes Control and Complications Trial (DCCT) showed significant relative risk reductions with intensive treatment (HbA_{1c} 7%) of 76% for the onset of retinopathy, 54% for retinopathy progression, 39% for nephropathy and significant reduction in neuropathy. Continuous benefit was suggested at lower levels but at the cost of a higher risk of hypoglycaemia. Evidence for microvascular benefit appeared greater than for macrovascular benefit because there were few macrovascular events in short-term follow-up, but time has demonstrated macrovascular benefit. Indeed, relative cardiovascular risk is very high in type 1 diabetes, particularly in younger patients, and all of the complications of type 2 diabetes (Case 2.23) may occur in type 1 diabetes.

Why does glycaemic control in diabetes tend to destabilise in hospital?

Stress causes a surge of counter-regulatory hormones including epinephrine (adrenaline), glucagon, cortisol and growth hormone.

Box 2.62 **Insulin in type 1 diabetes**

Insulin has a natural background basal release with prandial surges. Thus glucose is normally tightly controlled.

Types of insulin

In the 1970s through to the 1990s, human insulins and recombinant human insulins (*Escherichia coli* purified insulin without C-peptide) began to replace animal insulins and are now available as short-, intermediate- or long-acting preparations:

- Short-acting insulins include human insulin (Actrapid) and recombinant analogues Asport (Novorapid) and Lispro (Humalog).
- Intermediate- and long-acting human insulins include Isophane (Insulatard or Humulin I) and Protamine, and recombinant analogues include Glargine (Levemir) and Determir (Lantus).
- Biphasic (premixed combinations of short- and intermediate-acting insulin) insulins include Novomix (30% Aspart/70% Protamine) and Humalog Mix 25 or 50 (25% or 50% Lispro/75% or 50% Protamine); human Mixtard 30/70 and Humulin M3 (Actrapid 30%/Isophane 70%) have been largely superseded.

Insulin regimens

Twice-daily biphasic regimens

- Biphasic insulins are easy to administer and adequate for many patients with type 2 diabetes and some with type 1 diabetes. However, they do not provide tight control and hypoglycaemia may occur late morning and overnight. Blood glucose measurements always reflect previous insulin, so for example a measurement of 5.1 at 17.30 hours means it is safe to give a teatime dose provided the patient will eat at 18.00; if there is concern about nocturnal hypoglycaemia, a 03.00 measurement may be useful; if, for example, it is 3.5, teatime insulin should be reduced. Initial requirements may be estimated by calculating the total number of units of short-acting insulin given over 24 hours delivered by sliding scale into around two-thirds of the requirement administered in the morning and one-third at night.

Basal bolus regimens

- Short-acting insulin before meals with a once-daily longer, intermediate-acting insulin offers tighter glycaemic control than a twice-daily regimen and more flexible mealtimes and lifestyle. Ultra-long-acting insulin analogues tighten basal control, although the ideal aim of a plasma glucose of 5.1–7.0 is seldom always achievable with any regimen.
- Traditional short-acting insulins like Actrapid have an onset of action of around 30 minutes, a peak at around 2 hours (i.e. they do not act rapidly and mealtimes must be predicted) and last for around 8 hours (i.e. missing a predicted meal can result in prolonged hypoglycaemia). Traditional intermediate- and long-acting insulins seldom provide 24 hours of continuous basal insulin. Isophane, for example, wanes at 12–16 hours. For these reasons, these insulin analogues are now generally preferred. Initial requirements of traditional insulins may be estimated by calculating the total number of units of short-acting insulin given over 24 hours and dividing this into four split doses: breakfast, lunch, teatime (short-acting insulin) and before bed (longer-acting insulin); without a 24-hour guide, an empirical dose of around 6–10 units four times daily may be used.
- Short-acting analogues (SAAs) such as Novorapid or Humalog are rapidly absorbed subcutaneously and very rapid acting, with an onset of action between 1 and 2 minutes. They can be administered at meal times (even during meals) to mimic endogenous prandial insulin release. They are metabolised from the system within 1–2 hours, reducing the risk of subsequent hypoglycaemia. Long-acting analogues (LAAs) such as Glargine or Detemir are more predictably absorbed with prolonged activity profiles and no pronounced peaks in activity. They mimic endogenous, fasting, 24-hour basal insulin. Tight glycaemic control can now be achieved with a combination of a once-daily LAA and SAAs at mealtimes, limiting blood glucose rises between meals and reducing the risk of hypoglycaemia between meals and overnight. Initial requirements may be estimated by calculating the total number of units of short-acting insulin given over 24 hours (e.g. 50 units); this number of units is then divided into fifths – two-fifths (20 units) is given as LAA and one-fifth (10 units) as SAA at each of breakfast, lunch and tea. A pre-breakfast blood glucose reading can be monitored weekly and if > 7.0, the LAA increased (it is important to get the LAA step right first of all) and then the SAA can be adjusted by 2–4 units with each meal if the blood measurement remains > 7.0.
- Isophane is still often used instead of a LAA in basal bolus regimens containing SAAs but may need to be given twice daily with SAAs (i.e. five daily injections needed).

Insulin dose adjustment

- As a general rule, insulin dose adjustments should be by at least 20% of total daily dose.

Other insulin modes

- Increasingly, insulin pumps with implantable glucose sensors may be used to deliver continuous short-acting insulin. Inhaled insulin was available between 2006 and 2008 but did not gain popularity.
- Insulin regimens in type 2 diabetes, in older people and combined with oral hypoglycaemic agents are discussed in Case 2.23 (Type 2 diabetes).

Why is hypoglycaemia dangerous?

The brain depends on a constant supply of glucose to function, neuronal activity declining at levels < 3.5 mmol/l and cognitive function at < 3 mmol/l. Alternative fuels such as lactate and ketones cannot be mobilised in time during acute insulin-induced hypoglycaemia.

How is hypoglycaemia normally detected?

The hypothalamus and other areas of the brain normally sense hypoglycaemia, initiating a generalised autonomic (sympathetic) response.

Table 2.49 Normal responses to hypoglycaemia

Approximate blood glucose (mmol / l) at which response starts	Response
3.7	Adrenaline release
3.5	Start of neuronal dysfunction Sweating, tremor, palpitations, hunger (autonomic symptoms)
3.0	Start of cognitive dysfunction
2.5	Confusion, loss of concentration, speech difficulty, odd behaviour, incoordination, occasionally focal neurological deficits (neuroglycopenic symptoms)
1.0	Coma or seizure
Sustained hypoglycaemia	Permanent brain damage

What is the normal response to hypoglycaemia?

The autonomic response is protective by both producing counter-regulatory hormone release (glucagon and the catecholamine epinephrine,which stimulate hepatic glucose release and reduce glucose uptake by fat and muscle) and generating symptoms that alert the individual (Table 2.49). Growth hormone and cortisol, also produced during hypoglycaemia, play a relatively minor role during insulin-induced hypoglycaemia.

How problematic is hypoglycaemia in diabetes?

Hypoglycaemia is a potential problem when aiming for tight glycaemic control. Major hypoglycaemia was experienced by 27% of intensively treated patients in the DCCT and only 2% of patients in the *UK Prospective Diabetes Study (UKPDS)* (Case 2.23 Type 2 diabetes) despite broadly similar levels of glycaemic control. In the UKPDS over the first 10 years, major hypoglycaemia rates varied depending upon treatment modality, but were highest at 2.3% for patients on insulin. Hypoglycaemia remains very common in older people who may eat little and still take their tablets. Long-acting analogues reduce the risk of hypoglycaemia but cause sustained hypoglycaemia when it does occur and effects may occur days after the last dose.

What are hypoglycaemia-associated autonomic failure (HAAF) and hypoglycaemic unawareness?

Difficulty recognising hypoglycaemia affects about 25% of patients with type 1 diabetes and almost 50% who have had the disease for over 20 years. In insulin-deficient diabetes, exogenous insulin levels do not fall as glucose levels fall and the integrity of counter-regulatory hormones assumes greater significance. The glucagon response begins to fail within the first year or two of type 1 diabetes and is generally absent after 5 years, the epinephrine response becoming the crucial line of defence. The epinephrine response itself, however, is progressively blunted by antecedent hypoglycaemia (usually later in disease than glucagon failure), as is hypoglycaemic awareness because of loss of sympathetic symptoms. This combination of glucagon and epinephrine failure and unawareness because of antecedent hypoglycaemia is known as HAAF. By shifting glucose thresholds downwards for the symptomatic and sympatho-adrenal responses (to a level of around 2.5 mmol/l), antecedent hypoglycaemia creates a self-perpetuating cycle of recurrent hypoglycaemia without warning symptoms and further blunting of counter-regulation. The cycle can be broken by scrupulous avoidance of hypoglycaemia, which restores epinephrine (but not glucagon activity) and demonstrates that hypoglycaemic unawareness is not caused by autonomic neuropathy but rather HAAF.

How is hypoglycaemia treated?

A conscious patient should be given 10 g of quick-acting glucose (two teaspoons of sugar, three dextrose tablets, 50 ml original Lucozade, jam or honey) followed by long-acting carbohydrate such as bread, biscuits or milk. An unconscious patient should receive 50 ml of 50% dextrose intravenously or 1 mg of intramuscular glucagon.

Can hypoglycaemia be predicted and prevented?

Predictors include previous severe hypoglycaemia, recurrent asymptomatic hypoglycaemia (often nocturnal), diabetes of long duration and intensified insulin therapy. Education is vital. Hypoglycaemic awareness is more likely when patients have autonomic symptoms (sweats, shakes, palpitations) but less likely for patients relying on neuroglycopenic symptoms (confusion, dysarthria, unsteadiness). For those with impaired awareness, more physiological insulin and relaxation of glycaemic targets (e.g. pre-meal 4 mmol/l and pre-bed 7 mmol/l) may help, and scrupulous avoidance of hypoglycaemia may break the HAAF cycle.

How would you tackle nocturnal hypoglycaemia?

Nocturnal hypoglycaemia affects over 50% of people taking insulin, and more physiological replacement with insulin analogues and matching replacement to carbohydrate intake may lessen the problem, as may a bedtime snack. Snacking between meals may also help patients with non-physiological insulin profiles. Overnight insulin should be reduced after an overactive day. Alcohol should be avoided to excess, and overnight insulin should sometimes be reduced.

Other than overly tight glucose control in diabetes, what other causes of hypoglycaemia are there?

Hypoglycaemia may occur as a result of hepatic or adrenal failure. Severe hypoglycaemia is more commonly due to a person taking excess insulin (or sulphonylurea) deliberately (or, exceptionally rarely, malicious institution by a third party) or an insulinoma. Detection of elevated insulin and C-peptide levels during hypoglycaemia will determine if there is excess exogenous insulin (C-peptide absent) or an insulinoma (insulin and C-peptide levels high). Sometimes tumours including ovarian cancers and pleural fibromas also induce hypoglycaemia by producing insulin-like growth factors. Steroids may be a helpful treatment.

What is hyperosmolar non-ketotic coma?

This is an insidious rise in glucose to often very high levels, which predisposes to thrombotic complications; it is more common in older people with unrecognised type 2 diabetes and may present with polydipsia, polyuria or confusion. Ketones are absent or minimally present as insulin is not completely deficient, present in sufficient amount to incorporate some glucose into organs and thus prevent switching to alternative ketotic pathway sources of energy. However, glucose levels build up slowly in the bloodstream to impressive levels with a high osmolarity. Treatment is rehydration, insulin and anticoagulation.

CASE 2.23 TYPE 2 DIABETES MELLITUS

Candidate information

Role

You are a doctor in the diabetes clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Lorna Dunne, aged 60 years
>
> Thank you for seeing this lady urgently in clinic. She was diagnosed with type 2 diabetes 10 years ago and has a small ulcer on her right big toe that has now turned gangrenous. She has a history of sensory neuropathy. Her total cholesterol is 5.9 mmol/l despite statin therapy. Her current medications are metformin 1 g b.d., isophane insulin 20 units before bed, simvastatin 40 mg, aspirin 75 mg and atenolol 50 mg, all daily.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Lorna Dunne is a 60-year-old retired pharmaceutical representative who was diagnosed with type 2 diabetes 10 years ago and has been on insulin at night for 2 years together with metformin. She now has a small ulcer on her right big toe, which has turned black and painful. She has a history of sensory neuropathy with numbness, and poor peripheral circulation, and is an ex-smoker of 20 cigarettes a day. She has high cholesterol despite simvastatin. Her previous history comprises angina on exertion and problems with obesity. She had laser eye surgery last year but has no visual impairment. She feels her diet is reasonable but admits that exercise is difficult on account of her neuropathy and that she spent much of her working life in the car. She is now horrified by the black toe. Her husband is unwell with back problems, and needs help with washing and dressing.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Elicit the range of symptoms and complications.** Presentation of type 2 diabetes is usually with symptoms of hyperglycaemia or cardiovascular disease (CVD) complications after many years of silent development. The classic presentation and features are outlined in Box 2.63.

Take a full history of events surrounding the foot ulcer, and for:

- Glycaemic control – home monitoring and knowledge of glycated haemoglobin (HbA_{1c})
- Blood pressure
- Lipid levels
- Microvascular complications
- Macrovascular complications.

Patient perspective

A self-management programme should aim to develop understanding of diabetes, and promote the specific diabetes (e.g. monitoring) and general self-management (e.g. goal setting) skills needed for effective self-management. Areas include: what diabetes is; means of managing diabetes; consequences and personal risk; monitoring and

Box 2.63 **Classic features and complications of type 2 diabetes**

Type 2 diabetes is traditionally a disease of middle-aged and older people but increasingly seen in younger people. Over 80% are overweight or obese. Onset is gradual, and first presentation may be a complication. It is not associated with ketoacidosis, and autoimmune markers are negative. A positive family history is common.

Microvascular complications (common to type 1 and 2 diabetes)

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy

Macrovascular complications (common to type 1 and 2 diabetes)

- Acute coronary syndrome
- Stroke
- Peripheral vascular disease

taking action (including hypoglycaemic awareness); food choices; physical activity; stress and emotion; and screening and complication surveillance.

Past medical history

Explore the history of angina, investigations performed and treatment.

Drug and allergy history

Beta blockers and diuretics are associated with a significantly increased incidence of diabetes, and the former exacerbate peripheral vascular disease.

Family history

A family history of type 2 diabetes is common.

Social history

Enquire about the needs of her husband were she to be admitted to hospital.

SUMMARY BOX – ASSESSMENT AND PLAN

- Vascular studies will be needed to determine arterial flow, with care by the multidisciplinary diabetic foot care team.
- Possible outcomes include discharge and medical management, admission for further investigations, toe amputation or, possibly electively, revascularisation surgery.

Discussion

What is the scale of the problem of type 2 diabetes?

The worldwide prevalence of diabetes continuously escalates. The International Diabetes Federation's e-atlas and regularly updated 'Diabetes Maps' from the US Centers for Disease Control and Prevention graphically illustrate the scale of the problem. Type 2 diabetes accounts for about 90% of all diabetes. It is a worldwide epidemic, tripling in prevalence over the last 30 years and affecting 6–8% of middle-aged to older adults in North America and Europe. The number of adults predicted to have diabetes by 2025 is 333 million, and it is increasingly a problem in South East Asia. Adolescent- and childhood-onset type 2 diabetes is increasingly recognised. The pandemic has major economic implications and the need is great for people to be physically active and have less easy access to energy-rich foods. Type 2 diabetes is strongly associated with obesity, physical inactivity and other risk factors for CVD, and may be part of the metabolic syndrome (Case 2.7).

What causes type 2 diabetes?

There is a strong albeit poorly understood genetic susceptibility, and environmental factors crucial to development include excessive food intake, obesity and physical inactivity. Type 2 diabetes is a chronic, progressive metabolic disorder characterised by insulin resistance and impaired secretion.

Insulin resistance

Insulin acts on cells in muscle, fat and liver by binding to membrane receptors and triggering a series of intracellular phosphorylation steps leading to glucose uptake, and effects on fatty acid and protein metabolism. In type 2 diabetes, basal hepatic glucose output is increased, suppression of hepatic glucose output after meals is impaired and insulin-induced glucose uptake in muscle and fat is reduced. Increased triglycerides and low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C), together with uric acidaemia and increased plasminogen activator inhibitor 1, are also effects of insulin resistance and increase CVD risk. Both the insulin molecule and cell receptors are normal, but intracellular pathways are aberrant after insulin binding. Insulin resistance leads to elevated insulin concentrations in contrast to type 1 and other forms of diabetes in which endogenous insulin is low or absent.

Beta-cell failure

Despite hyperinsulinaemia, the beta cell response to hyperglycaemia is inadequate and insulin secretion is always abnormal once type 2 diabetes is fully established. Insulin secretory responses to meals are severely blunted, with post-prandial hyperglycaemia early in disease leading to fasting hyperglycaemia as disease progresses and insulin concentrations cannot overcome hepatic insulin resistance. Ultimately, hyperinsulinaemia gives way to beta-cell failure and hypoinsulinaemia.

How is diabetes care best coordinated?

Diabetes is a long-term condition requiring a multidisciplinary approach across health settings that should consider the areas outlined in Table 2.50.

Table 2.50 Diabetes care

Patient-centred care and patient education	Structured, individually tailored self-management plan and education programme
Dietary advice	Nutritional advice
Assessment and treatment of blood glucose	Individually tailored targets for HbA_{1c} (general target 6.5, measured every 2–6 months) and self-monitoring as part of the self-management plan
Management of cardiovascular disease risk	Estimation of risk not recommended as most with type 2 diabetes at high risk Blood pressure and lipid-lowering treatment
Diabetic nephropathy	Measurement of albumin–creatinine ratio on first-pass morning urine (or spot urine) annually; if > 2.5 mg / mmol for men or > 3.5 mg / mmol for women or if glomerular filtration rate abnormal, non-diabetic renal disease should also be considered If diabetes likely cause, angiotensin-converting enzyme or angiotensin receptor blocker
Diabetic neuropathy	Annual review of symptoms Specialist management of foot problems Review issue of erectile dysfunction Consideration of possible contributory damage to the sympathetic nervous system if impaired hypoglycaemic awareness, and autonomic dysfunction contributing to orthostatic hypotension, diarrhoea or bladder emptying difficulties
Diabetic retinopathy	Retinal screening at least annually (25–30% with type 2 diabetes have retinopathy at presentation, correlating with 7 years of antecedent hyperglycaemia)

HbA_{1c}, glycated haemoglobin.

Why is glycaemic control in type 2 diabetes important?

Type 2 diabetes mellitus is a complex chronic condition associated with hyperglycaemia and long-term end-organ damage. This damage, due to exposure to hyperglycaemia, leads to increased risk of CVD and excess mortality. Advanced glycation end products are of pathogenic importance. Glucose binds with protein to produce glycated proteins such as HbA_{1c}. The property of these proteins is altered by, for example, cross-links, and this is very important for molecules that are not readily renewed such as collagen, which become advanced glycation end products.

Acute glycaemic management

Short-term glycaemic control in hospitalised patients might be expected to improve well-being, reduce infection rates, aid wound healing, prevent severe hyperglycaemia and reduce vascular complications. The Dextrose Insulin and Glucose in Acute Myocardial Infarction (DIGAMI) study showed that tight control at the time of infarction and for 3 months reduced 3-year mortality by 11%, but other studies have been conflicting and in DIGAMI 2 the benefits of DIGAMI were not replicated.

The UK Prospective Diabetes Study (UKPDS) and long-term gylcaemic control

The UKPDS was a 20-year study of over 5000 patients with type 2 diabetes. It showed that the intensive glycaemic control (average HbA_{1c} 7.0%) produces considerably fewer microvascular complications (Table 2.51) than conventional control (average HbA_{1c} 7.9%). Good glycaemic control also reduces the risk of stroke and myocardial infarction. There were no differences in glucose control or microvascular endpoints between patients treated with chlorpropamide, glibenclamide or insulin. Metformin, used as primary therapy for overweight patients, reduced microvascular and macrovascular endpoints at similar levels of glucose control to other therapies, and was the only therapy not associated with weight gain. Improving glycaemic control with insulin or a sulphonylurea had only marginal macrovascular benefit but an explanation for this may be that longer term follow-up was needed; UKPDS-PTD (post-trial monitoring data) in 2008 on macrovascular outcomes 10 years on reported that tight blood glucose control with sulphonylurea and insulin versus conventional therapy as well as metformin versus conventional therapy have reduced myocardial infarction and all-cause mortality. UKPDS also showed that controlling hypertension had an important impact on macrovascular events. UKPDS also showed that HbA_{1c} tended to rise every 5 years by around 1% even in tightly controlled patients, perhaps reducing the temptation to 'blame' patients or doctors for disease progression.

Table 2.51 Effects of a 1% reduction in glycated haemoglobin on complications in type 2 diabetes

Complication	Risk reduction (%)
Albuminuria at 12 years	33
Retinopathy at 12 years	21
Microvascular disease	25
Myocardial infarction	16
Any diabetes-related complication	12

Table 2.52 Oral hypoglycaemic agents

Drugs	Action	Indications	Dose	Advantages	Side effects
Metformin	Reduces hepatic gluconeogenesis Enhanced peripheral utilisation of glucose Only effective in presence of endogenous insulin (some residual beta-cell function)	First line in overweight or obese Suitable monotherapy	500 mg b.d. to optimum 850 mg t.d.s. if tolerated Available in modified release formulation	No weight gain Seldom hypoglycaemia May be cardioprotective (UKPDS)	Gastrointestinal (20%) – diarrhoea, nausea – may arise after years of treatment Lactic acidosis (contraindicated if acutely ill, renal failure – (creatinine > 150 μmol / l, decompensated liver disease, severe heart failure) Vitamin B12 deficiency
Sulphonylureas, e.g. gliclazide	Insulin secretagogues (potentiate insulin release) by binding receptors on beta cells and closing potassium channels Long or short acting	Normal/ underweight (metformin may be considered) Suitable monotherapy		No lactic acidosis	Weight gain Hypoglycaemia (low incidence but dangerous and sometimes prolonged)
Thiazolidinediones 'Glitazones', e.g. rosiglitazone, pioglitazone	Activate nuclear peroxisome proliferator-activated receptor γ in liver, muscle and fat; this controls expression of genes regulating metabolism Improves insulin sensitivity, especially in skeletal muscle Slow onset of action	Place in treatment controversial but mechanism of action suggests they may be appropriate in patients intolerant of metformin Contraindicated with insulin	Pioglitazone 15–45 mg o.d. Rosiglitazone 4–8 mg o.d. or b.d.	Improve HbA_{1c} by up to 1.5% Pioglitazone especially lowers triglcerides and raises HDL	Fluid retention (contraindicated in heart failure; caution in renal or liver disease) Increased fracture risk (it seems not all glitazones are equal – evidence pioglitazone significantly reduced death, myocardial infarction and stroke was not reproduced by rosiglitzone, which may also increase the risk of myocardial infarction; despite adverse liver effect concerns, in many cases liver function improves, probably through reduced non-alcoholic fatty liver disease)
Prandial glucose regulators, e.g. repaglinide, nateglinide	Induce rapid post-prandial insulin release (target early phase insulin release) Ultra short acting Taken with meals; may be useful if unpredictable lifestyle	Add-on therapy	Repaglinide 0.5 mg pre-meals to maximum 16 mg / day Netaglinide 60 mg t.d.s. to maximum 180 mg t.d.s.	Early phase insulin release is one of the earliest malfunctions in type 2 diabetes Well tolerated Reduce HbA_{1c}	Hypoglycaemia
α-glucosidase inhibitors, e.g. acarbose	Attenuate carbohydrate absorption by inhibiting mucosal enzymes that hydrolyse complex to simple sugars	Monotherapy or combined with metformin or sulphonylurea	25–100 mg t.d.s.	No metabolic side effects	Excessive abdominal bloating, flatulence and pain Less impact on HBA_{1c} (UKPDS)

HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; UKPDS, UK Prospective Diabetes Study.

The ACCORD study showed that those with high HBA_{1c} levels (> 8.5%) who struggle to lower it are at mortality risk from intensive glucose lowering to achieve levels < 6%.

Which groups of hypoglycaemic agent are used in type 2 diabetes?

Management of type 2 diabetes is complex and aims to prevent and reduce the impact of complications by means of a healthy lifestyle, controlling blood pressure and blood lipids, and lowering blood glucose concentrations. While diet and exercise and weight loss remain more effective than pharmacotherapy, only a minority of patients achieve optimal control through lifestyle efforts alone. As well as traditional oral hypoglycaemic agents (Table 2.52), in recent years new drugs for glycaemic control have become available, including long-acting insulin analogues, and glucagon-like peptide-1 (GLP-1) mimetics and dipeptidylpeptidase-4 (DPP-4) inhibitors (Box 2.64).

Box 2.64 **Glucagon-like peptide (GLP)-1 mimetics and dipeptidyl peptidase 4 (DPP4) inhibitors**

GLP-1 mimetics or incretin mimetics (e.g. exenatide, liraglutide) and DPP4 inhibitors or incretin enhancers (e.g. sitagliptin and vildagliptin) represent a relatively new class of agents for glycaemic management.

How they work

GLP-1 is a gut hormone that stimulates insulin secretion; together with the related hormone, glucose-dependent insulotropic polypeptide (GIP), it is responsible for the incretin effect, the augmentation of insulin secretion with oral administration of glucose (patients with type 2 diabetes typically have little or no incretin-mediated augmentation of insulin owing to decreased secretion of GLP-1 and loss of the insulotropic effects of GIP). GLP-1 is rapidly degraded by the enzyme DPP4. GLP-1 mimetics increase insulin secretion, inhibit glucagon secretion, and delay gastric emptying, so reducing appetite and food intake. DPP-4 inhibitors stabilise concentrations of endogenous GLP-1 and increase insulin secretion.

How they are used

They are titrated to glucose with relative ease of use and monitoring. Advantages are avoidance of hypoglycaemia (when used alone, but this may be insufficient to reach target glycaemic control) and weight loss, unlike with insulin, which is anabolic. GLP-1 mimetics have a greater glycated haemoglobin-lowering effect than DPP4 inhibitors, but at the expense of inconvenience in delivery (subcutaneous versus oral administration) and greater (mainly gastrointestinal) side effects.

How would you approach using glycaemic control agents in type 2 diabetes in practice?

A stepwise approach is used.

First-line therapy – metformin

A joint consensus statement from the American Diabetes Association and European Association for the Study of Diabetes emphasises metformin as the preferred option for initial monotherapy.

Second-line therapy – sulphonylureas, DPP-4 inhibitors, thiazolidinediones

Owing to progressive beta-cell failure, most patients eventually fail monotherapy. The consensus statement does not specify second-line therapy, but National Institute for Health and Clinical Excellence recommendations are as follows.

Sulphonylureas

It is usual to use a sulphonylurea second-line if metformin alone is inadequate, or a sulphonylurea as monotherapy if metformin is not tolerated or contraindicated.

DPP-4 inhibitors and thiazolidinediones

- A DPP-4 inhibitor or thiazolidinedione should be considered second-line with metformin instead of a sulphonylurea when blood glucose control remains or becomes inadequate (HbA$_{1c}$ ≥ 6.5% or higher level agreed with the individual), if there is serious risk of hypoglycaemia or a sulphonylurea is not tolerated or contraindicated (e.g. severe renal impairment).
- If metformin is not tolerated or contraindicated (e.g. renal impairment), a DPP-4 inhibitor or thiazolidinedione should be considered second-line with a sulphonylurea when blood glucose control remains or becomes inadequate.

A DPP-4 inhibitor or a thiazolidinedione should be continued only if a beneficial response occurs (reduction of ≥ 0.5 in HbA$_{1c}$ in 6 months). A thiazolidinedione is contraindicated in heart failure or where there is a high risk of fracture. A DPP-4 inhibitor may be preferable to a thiazolidinedione if further weight gain would provoke serious problems, or if a thiazolidinedione is not tolerated or contraindicated. A thiazolidinedione may be preferable to a DPP-4 inhibitor if reduced insulin sensitivity is likely or if a DPP-4 inhibitor is not tolerated or contraindicated. Sometimes either a DPP-4 inhibitor or a thiazolidinedione may be suitable, the choice determined by patient preference.

Third-line therapy – sitagliptin, GLP-1 mimetics

- If metformin with a sulphonylurea does not adequately control blood glucose (HbA$_{1c}$ ≥ 7.5% or higher level agreed with individual) and insulin is unacceptable or inappropriate (e.g. employment, social reasons, recreational problems related to hypoglycaemia, injection anxieties, other personal matters, obesity) sitagliptin or a thiazolidinedione may be considered as third-line treatment.
- A GLP-1 mimetic (exenatide, liraglutide) may be considered as third-line treatment (HbA$_{1c}$ ≥ 7.5% or higher level agreed with individual) to metformin and a sulphonylurea if a person has a body mass index (kg/m^2) ≥ 35.0 and specific psychological or medical problems associated with high body weight, only continued if a beneficial response occurs (reduction of ≥ 1.0 in HbA$_{1c}$ and weight loss of at least 3% of initial body weight over 6 months).

The role of insulin

Box 2.65 describes the indications for insulin use in type 2 diabetes. Combining pioglitazone with insulin may be considered where there has been marked glucose lowering with a thiazolidinedione or where high-dose insulin does not inadequately control blood glucose.

What other measures are important in reducing complications in type 2 diabetes?

Apart from glycaemic management, it is essential to target other contributors including diet and weight, smoking, blood pressure and lipids effectively. Atherosclerosis is a complex pathological process that is accelerated in diabetes and accounts for a higher proportion of total mortality than in the general population. It results from

Box 2.65 **Insulin in type 2 diabetes**

It is common to use insulin with other agents in type 2 diabetes, although it is anabolic, which may be of concern in obesity. Typically a patient may be on maximal oral hypoglycaemic agent therapy (e.g. metformin 2 g with a second/third-line agent) and insulin is substituted for the second/third-line agent, often contraindicated with insulin. Types of insulin, and some of the regimens used in type 2 diabetes, are as for type 1 diabetes described in Box 2.62, Case 2.22 (Type 1 diabetes).

Indications for insulin in type 2 diabetes

- People on dual oral therapy who are markedly hyperglycaemic, in preference to adding another agent
- Poor glycaemic control associated with marked symptoms and weight loss (suggests beta-cell failure)
- Poor glycaemic control despite concordance with treatment, suboptimal glycaemic control with high risk of complications (young age or established vascular complications)
- Intolerance of other agents
- Temporarily in acute coronary syndromes, acute illness, surgery and alongside short-term corticosteroid use.

Insulin can be thought of as anticipating or following the level of glycaemic control. Tailoring short-acting insulin doses before meals to the amount expected to eat is anticipating the effect of food on plasma glucose. At the other extreme, infused insulin is chasing the tail of glucose excursions. Sliding-scale insulin is thus inappropriate in patients well enough to eat where an anticipating regimen is needed and a basal bolus regimen can both follow glucose but also anticipate rises after meals.

Insulin regimens

Twice-daily biphasic regimens

These may be considered as in type 1 diabetes.

Once-daily intermediate or long-acting human insulin or long-acting insulin analogue (LAA) regimens

- Once-daily Isophane, best given at bedtime, alongside daytime oral hypoglycaemic agents, is a traditional way of introducing insulin, aiming for a dose that produces a fasting glucose of around 6.0. Potential problems are a tendency to hyperglycaemia later in the day and nocturnal hypoglycaemia, especially with higher doses (> 30 units). Twice-daily Isophane as basal insulin was sometimes used to prevent hyperglycaemia.
- A LAA, giving respectable glucose levels after about 2 hours lasting for 24 hours with predictable absorption, now seems much more preferable to Isophane, especially because of the variable effects from Isophane. Many diabetologists now regard metformin and a LAA as a regimen of choice. The same number of units of LAA is used as once-daily Isophane but 20% less than a twice-daily Isophane regimen; in general 10–12 units of LAA is a reasonable starting dose. However, LAAs are still not used routinely in type 2 diabetes and National Institute for Health and Clinical Excellence guidelines recommend a LAA as an alternative or substitute for human insulin for: those who need help to administer injections for whom use of a LAA would reduce injections from twice to once daily; those who cannot use devices for administering human insulin (or variable effect from Isophane – variable absorption or poor mixing, whereas LAAs are premixed); those who experience severe or symptomatic hypoglycaemia or who do not reach their target glycated haemoglobin because of hypoglycaemia; those who would otherwise need twice-daily basal insulin injections in combination with oral glucose-lowering drugs

Basal bolus regimens

- Basal bolus regimens are usually reserved for type 1 diabetes, but may be used in active, younger patients with type 2 diabetes or in unwell patients with type 2 diabetes.

one or more established and/or ‘novel’ risk factors. Type 2 diabetes is characterised by obesity and insulin resistance and frequently associated with hypertension and dyslipidaemia. Other predictors of cardiovascular risk include microalbuminuria, elevated B-type natriuretic peptide, hypoadiponectinaemia, vitamin D deficiency and testosterone deficiency. Endothelial dysfunction is an important antecedent of many complications of diabetes and is present in states of pre-diabetes.

Recent years have seen a paradigm shift in understanding the best strategies to lower cardiovascular risk in type 2 diabetes. In the past, considerable emphasis was placed on reduction of plasma glucose and there were misplaced perceptions of benefit from aspirin in all patients. There is now overwhelming evidence that lowering cholesterol with statin therapy and lowering blood pressure with antihypertensive agents, at least to a systolic value of 130 mmHg, are the keys to success in achieving such benefits. Trial and meta-analytical evidence has shown that aspirin for primary prevention of vascular events is probably unwarranted, intensive glucose lowering achieves limited reductions in CVD, and fibrate therapy has no clear benefit with regard to reducing vascular events in type 2 diabetes despite favourable changes in lipid subfractions.

Blood pressure

Elevated blood pressure (> 140/90 mmHg) is twice as common in diabetes and greatly increases an already increased cardiovascular risk. The combination of hypertension and diabetes doubles the risk of developing microvascular and macrovascular complications, and doubles mortality compared with non-diabetic people with hypertension. Evidence for blood pressure reduction is largely from trials that included people with diabetes shown to reduce or prevent major cardiovascular events including heart failure, cardiovascular death and total mortality. There is also evidence of reduced progression to retinopathy and nephropathy in people with diabetes but without CVD. Blood pressure targets are < 130/80 mmHg, possibly lower in diabetic nephropathy, the greater the reduction the greater the benefit and there appears to be no threshold below which risk no longer declines. Strict blood pressure control is the most important factor preventing diabetic nephropathy and its progression. Almost all patients need a combination of drugs and the evidence for nephroprotection is greatest with renin–angiotensin system blockade.

Lipid lowering

Diabetic dyslipidaemia is characterised by high LDL-C and triglycerides and low HDL-C. Covert hypothyroidism may coexist with diabetes and produce similar dyslipidaemia. Evidence for lipid lowering in diabetes reducing cardiovascular risk is largely from study subgroup analyses including people with diabetes. More recent trials exclusively in diabetes have shown significant reductions in cardiovascular events in people with diabetes comparable to those without diabetes. The Heart Protection Study included more people with type 1 and type 2 diabetes than previous studies combined and showed that patients with type 2 diabetes, one other risk factor for coronary heart disease and a total cholesterol > 3.5 mmol/l had 33% fewer CVD events (coronary or stroke) with 40 mg simvastatin. ASCOT-LLA similarly had a large diabetes cohort and the 19% non-significant reduction in fatal coronary heart disease and myocardial infarction probably reflected reduced statistical power because it was stopped early. CARDS evaluated statin therapy exclusively in diabetic patients and compared atorvastatin 10 mg with placebo and was terminated early because the 37% reduction in CVD events (reductions in acute coronary heart disease events by 37% and stroke by 48%) was larger than that observed in the Heart Protection Study. All patients with diabetes should therefore be considered for statin therapy, with a minimum dose of simvastatin 40 mg or equivalent.

What do you know about diabetic nephropathy?

Diabetic nephropathy is summarised in Box 2.66.

Box 2.66 **Diabetic nephropathy**

Definition

By convention, this is an albumin excretion rate (AER) > 300 mg/24 hours in a person with diabetes of more than 5 years and concomitant retinopathy, in the absence of urinary tract infection, other renal disease or heart failure. Urinary AER in a timed collection should only be determined if urinary albumin concentration or albumin–creatinine ratio exceed the normal range (Case 2.26), and then confirmed on two subsequent samples. All patients should be screened annually.

Types of diabetic nephropathy

Diabetic nephropathy in type 1 diabetes is usually of classic type, rare in the first 10 years, peaking at 3% per year at 15 years and declining slowly thereafter such that after 40 years' duration it is only 1% per year. Those without it then are at low risk. In type 2 diabetes, the classic form with associated retinopathy and progression from microalbuminuria to proteinuria is common, but an atypical form without retinopathy and with minimal or no proteinuria occurs.

Risk factors for diabetic nephropathy

Suboptimal glycaemic control and a higher blood pressure are particularly important risk factors for development of diabetic nephropathy.

Why diabetic nephropathy is important

Diabetic nephropathy is a major cause of morbidity and mortality in both type 1 and type 2 diabetes. This is principally from coronary artery and other forms of cardiovascular disease, and particularly from heart failure, the incidence of which is about 15-fold greater in patients with diabetic kidney disease. Diabetes also remains the single most common cause of end-stage renal failure.

Increased glomerular filtration, renal blood flow and hypertrophy precede diabetic nephropathy and are reversible with good glycaemic and blood pressure control. Diabetic nephropathy can usually be detected many years before development of advanced renal failure through the detection of raised urinary AER – microalbuminuria. This allows time for the intensive treatment of glycaemic control, blood pressure and other cardiovascular risk factors to reduce the morbidity and mortality. Significant structural damage accompanies microalbuminuria, often with hypertension, and although the glomerular filtration rate (GFR) may not be affected until the high microalbuminuria range is reached, microalbuminuria is strongly predictive of cardiovascular disease death, especially in older patients with type 2 diabetes.

In type 1 diabetes, proteinuria developing after a very long duration more likely reflects cardiovascular disease than diabetic nephropathy. Persistent albuminuria or overt diabetic nephropathy is usually accompanied by atherosclerosis and, untreated, a relentless decline in GFR with death after an average 7–10 years.

Treatment

Good glycaemic control can prevent diabetic nephropathy but there is less evidence that it prevents progression once established. Strict blood pressure control is the mainstay of treatment, with blockade of the renin–angiotensin system.

In type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors reduce progression from microalbuminuria to overt nephropathy and from overt nephropathy to end-stage kidney disease.

In type 2 diabetes, ACE inhibitors reduce mortality in those with microalbuminuria, and angiotensin receptor blockers (ARBs) reduce progression from microalbuminuria to overt nephropathy and progression thereof. There is no evidence that ARBs reduce mortality, however, and so ACE inhibitors remain the first-line treatment for all forms of diabetic nephropathy in types 1 and 2 diabetes, although some favour ARBs in type 2 diabetes. The combination of an ACE inhibitor and ARB may be beneficial in thwarting nephropathy, but large studies are lacking.

Box 2.67 **Diabetic neuropathy**

Diabetic polyneuropathy

This is one of the commonest long-term complications of diabetes and the commonest form of neuropathy in the developed world. It encompasses a number of neuropathic syndromes, the commonest of which is chronic distal symmetrical polyneuropathy, also known as diabetic peripheral neuropathy (DPN). DPN is a cause of considerable morbidity, including foot ulceration, amputations and neuropathic pain, and is associated with cardiovascular disease and increased mortality. Risk factors for DPN include poor glucose control and markers of macrovascular disease, such as hypertension. There is strong evidence for nerve ischaemia as the cause. Painful DPN affects 15–26% of all people with diabetes and can lead to considerable disability. First-line therapies for painful DPN are tricyclic antidepressants, serotonin norepinephrine (noradrenaline) reuptake inhibitors or anticonvulsants such as pregabalin or gabapentin.

Diabetic autonomic neuropathy

This results in considerable morbidity and reduction in quality of life, and is associated with increased mortality. It may involve cardiovascular, gastrointestinal, urogenital, pupillomotor, thermoregulatory and sudomotor function.

Other neuropathies

These include acute focal neuropathy, femoral neuropathy and diabetic amyotrophy.

What do you know about diabetic neuropathy?

Diabetic neuropathy is summarised in Box 2.67.

What do you know about the diabetic foot?

Foot problems remain the commonest cause of hospital admission amongst patients with diabetes in Western countries. As many as 50% of older patients with type 2 diabetes have risk factors for foot problems.

Complications of diabetic neuropathy in the foot include ulceration, callus formation, deformity, and Charcot's joints and wasting. Sensory neuropathy leads to unawareness of injury, autonomic neuropathy leads to anhidrosis with dry, fissuring skin and susceptibility to infection. Motor neuropathy leads to altered muscle tone and deformity, often with pes cavus and pressure areas.

The lifetime risk of a patient with diabetes developing an ulcer is 25%, and up to 85% of all lower limb amputations in diabetes are preceded by foot ulcers. The key to management of diabetic neuropathic foot ulceration is aggressive debridement with removal of callus and dead tissue, followed by application of some form of cast to offload the ulcer area. Most ulcers will heal if pressure is removed from the ulcer site, if the arterial circulation is sufficient and if infection is managed and treated aggressively. Any patient with a warm swollen foot without ulceration should be presumed to have acute Charcot neuroarthropathy until proven otherwise.

The approach to reducing ulceration is regular screening, patient education and a team approach to management, both in the community and in hospital. Diabetic foot clinics utilise the expertise of diabetologists, surgeons, chiropodists and physiotherapists. Radiological investigations include plain radiographs for evidence of osteomyelitis (e.g. erosion, periostial reaction), nuclear imaging, computed tomography and magnetic resonance imaging, the last being good for detecting extent and localisation of infection and inflammation.

What do you know about sexual dysfunction in diabetes?

Erectile dysfunction affects over a third of diabetic men, caused by failure of nitric oxide-mediated smooth muscle relaxation of the corpus cavernosum secondary to endothelial dysfunction and autonomic neuropathy. Phosphodiesterase type 5 inhibitors are first-line treatment.

Eye problems

CASE 2.24 VISUAL LOSS

Candidate information

Role

You are a doctor in the diabetes clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr John Knight, aged 80 years

Thank you for seeing this gentleman urgently. He has had several episodes of zig-zag vision over the last few months. He has type 2 diabetes for which he takes metformin, aspirin, simvastatin, perindopril and bendroflumethazide. He had a stroke 3 years ago from which he made a full recovery. I wonder if he could have worsening diabetic retinopathy or if these are TIAs.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr John Knight is an 80-year-old widowed man with type 2 diabetes mellitus who has experienced several episodes of disturbed vision over the past 3 months – sometimes blurred vision, sometimes glare whilst driving and sometimes indistinct letters when reading. Both eyes appear to be affected. Episodes resolve spontaneously and last for up to an hour. There is no associated limb weakness or speech difficulty or altered sensation. He feels his vision has generally become less distinct over the past year. He is still driving. He has a past medical history of type 2 diabetes but since a stroke with right arm weakness 3 years ago he has been very strict about keeping himself healthy. He made a full recovery from his stroke. He takes metformin 850 mg twice daily, asprin 75 mg, simvastatin 40 mg, perindopril 4 mg and bendroflumethazide 2.5 mg. He monitors his blood glucose and knows that his glycated haemoglobin (HbA_{1c}) is 7.5%. He monitors his blood pressure and average readings are around 140/70 mmHg. His total cholesterol is 4.8 mmol/l. He has background diabetic retinopathy and at retinal screening 6 months ago the ophthalmology team were happy.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

■ **Explore visual loss.** Visual loss may be acute or gradual, and affect one or both eyes. It may commonly be due to the causes listed in Table 2.53.

■ **Ask about colours or shapes.** Patients frequently complain of *spots* in their vision. It is important to differentiate between *flashing lights* (a sign of incipient retinal detachment) and *floaters* (opacities in the vitreous). Haloes (a waterlogged cornea breaks up white light as does the sky after a rainstorm, and because of the shape of the cornea the 'rainbow' is round) may be a sign of incipient acute glaucoma. Wavy lines on a grid may be due to wet age-related macular degeneration.

Table 2.53 Causes of visual loss

Type of visual loss	Causes
Gradual loss of central vision in one or both eyes	Cataract Age-related macular degeneration
Gradual loss of peripheral vision in one or both eyes	Primary open angle glaucoma Retinal detachment Retinitis pigmentosa
Acute loss of central vision in one eye	Optic neuritis
Acute loss of vision (total or variable distribution) in one eye	Central / branch retinal vein occlusion Central retinal artery occlusion Retinal detachment Retinal haemorrhage Amaurosis fugax
Acute homonymous visual field loss	Stroke

Patient perspective

He is extremely well motivated and an excellent historian.

Past medical history

His past medical history of stroke and diabetes immediately alert you to diabetic retinopathy or transient ischaemic attacks (TIAs), but the bilateral symptoms suggest alternative diagnoses.

Drug and allergy history

He is concordant with a good range of secondary vascular prophylaxis.

Family history

Relevance here is unlikely.

Social history

He should not drive until TIAs have absolutely been excluded and until his vision has been fully assessed.

SUMMARY BOX – ASSESSMENT AND PLAN

- Likely diagnoses are cataracts (related or unrelated to his diabetes) or age-related macular degeneration or a combination of both. Glaucoma is possible. He should certainly be referred to an ophthalmologist.
- Transient ischaemic attacks seem less likely, but if there is concern about focal neurological symptoms/amaurosis fugax then a carotid Doppler study should be undertaken promptly.
- Hypoglycaemic episodes are possible.

Discussion

What is glaucoma?

This is described in Case 5.30.

What are the visual requirements for driving?

These are described in Case 4.49.

Renal and metabolic problems

CASE 2.25 ACUTE KIDNEY INJURY

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner

(GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr Philip Martin, aged 72 years

Thank you for admitting this gentleman who appears to be oligoanuric. He seems to be developing oedema in his ankles and his blood pressure, usually well controlled, is 190/110 mmHg. His blood tests show a creatinine of 750 μmol/l and a potassium of 6.7 mmol/l. Urinalysis shows a trace of protein but no blood. His creatinine was 130 μmol/l a year ago, at which time he also had a normal renal ultrasound. He has a past medical history of hypertension for which he takes ramipril and bendroflumethiazide, and benign prostatic hypertrophy under surveillance.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Philip Martin is a 72-year-old man who for the last 2 weeks has noticed difficulty passing urine and gradual swelling of his ankles. He now feels uncomfortable suprapubically and has been admitted to hospital. He has a history of hypertension for which he takes ramipril 10 mg and bendroflumethiazide 2.5 mg, both daily. Last year he was investigated for possible prostate cancer, which turned out to be benign. He normally has a little trouble with urinary flow but nothing as problematic as this week. He feels generally weak and lethargic. He put off seeing his doctor because his wife has moderately severe Alzheimer's dementia and there is no one to look after her. He is a very active man who finally decided he must see his doctor because his symptoms had become so severe.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Most acute renal failure, now termed acute kidney injury (AKI), is managed by general physicians; it is essential to be able to assess and treat AKI in the first few hours of admission and know when to seek nephrology input. Over recent years it has been recognised that even small degrees of renal dysfunction are associated with worse patient outcomes. Unfortunately, as confirmed by the UK's National Confidential Enquiry into Patient Outcome and Death, recognition is often delayed and management frequently sub-optimal. Recogntion of risk factors, accurate history taking, careful examination and meticulous monitoring of volume balance are enough to reverse this process, although AKI does present a unique set of metabolic derangements that, if untreated, will result in death. AKI is defined in Box 2.68. These definitions, proposed by the Acute Dialysis Quality Initiative and the Acute Kidney Injury Network, aimed to promote earlier detection and recognition of AKI triggering appropriate treatment prior to progressive injury and kidney failure. The application of these definitions in more than 500 000 patients has validated the increased risk of mortality associated with developing AKI and indicated that the incidence of AKI in hospitalised patients may be as high as 18%. The definitions have recently been harmonised by the Kidney Diseases: Improving Global Outcomes International Guideline Group.

Box 2.68 Definition of acute kidney injury (AKI)

AKI is present when one of the following criteria is met:

- Serum creatinine rises by ≥ 26 μmol/l within 48 hours
- Serum creatinine rises ≥ 1.5 fold from the reference value, which is known or presumed to have occurred within 1 week
- Urine output is < 0.5 ml/kg/h for > 6 consecutive hours (the use of urine output criteria for both diagnosis and staging of AKI has been less well studied; clinical judgement is needed in assessment, and recognition that patients may develop oliguric or non-oliguric AKI)

If a reference serum creatinine value is not available within 3 months (acceptable up to one year) and AKI is suspected serum creatinine should be repeated within 24 hours, and a reference serum creatinine value can be estimated from the nadir serum creatinine value if the patient recovers from AKI.

Clinical assessment should consider firstly patient safety, secondly risk factors and possible causes, and thirdly the effects of AKI.

■ **Ensure safety.** Before full assessment, immediate management of hyperkalaemia (below), hypoxia (usually due to pulmonary oedema) or restoration of circulating volume may be needed.

■ **Consider risk factors and possible causes.** These are summarised in Box 2.69 and Box 2.70.

■ **Consider effects.** The following areas should be considered.

Symptoms. Patients are usually asymptomatic until advanced stages and so lack of symptoms is not a reassurance. The syndrome of uraemia is complex and results from retention of multiple substances, many not yet established. The role of urea in uraemic syndrome is uncertain. Uraemic symptoms may include anorexia, nausea and vomiting, cramps and restless legs, peripheral neuropathy symptoms, cognitive disturbance and drowsiness, hiccups, itch, pericarditis symptoms or myoclonus.

Fluid status. The history is a good guide to fluid status. A history of vomiting and diarrhoea suggests dehydration while shortness of breath or ankle swelling suggest fluid overload. The presence of any oedema suggests that a patient is at least a few litres overloaded. Assessment of fluid status is outlined in Box 2.71. Early chronic kidney disease (CKD) may cause nocturia (attempts to remove toxins), tubular dysfunction and sometimes polyuria. Oligoanuria is a late sign in CKD but usual in AKI.

Box 2.69 **Risk factors for developing acute kidney injury**

- Age > 75 years
- Chronic kidney disease (especially stage 3 or below)
- Heart failure
- Atherosclerotic peripheral vascular disease
- Liver disease
- Diabetes mellitus
- Nephrotoxic medication
- Hypovolaemia
- Sepsis

Box 2.70 **Causes of kidney disease (acute kidney injury (AKI) and chronic kidney disease (CKD))**

Patients presenting with renal disease may present with AKI, sub-acute renal disease or CKD. In all cases the following lists of causes should be considered and combinations of causes are common.

Pre-renal causes

Pre-renal AKI is an expected physiological response to:

- Hypovolaemia, e.g. haemorrhage, gastrointestinal losses, renal losses, burns
- Hypotension – cardiogenic shock or distributive shock, e.g. sepsis/the systemic inflammatory response syndrome, anaphylaxis
- Renal hypoperfusion, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renal artery stenosis
- Oedematous states, e.g. heart failure, cirrhosis, nephrotic syndrome.

Pre-renal AKI may compound CKD, as in heart failure and renovascular disease, where glomerular filtration rate may fall sharply owing to worsening cardiac output or nephrotoxic drugs.

Renal causes

The kidney comprises glomeruli, tubules and interstitium, and blood vessels. Disease in any of these can cause renal failure.

Glomerular disease

- Glomerulonephritis (GN) and primary glomerular diseases are discussed in Case 2.27. Most causes lead to CKD, but rapidly progressive GN because of vasculitis, lupus or glomerular basement membrane disease may cause AKI.
- Secondary glomerular diseases are common worldwide, e.g. bacterial, viral (especially hepatitis and human immunodeficiency virus), tumours and drugs, often presenting with nephrotic syndrome
- Diabetic nephropathy affects more than one-third of patients with type 1 diabetes and an ever-increasing proportion of patients with type 2 diabetes, and is the single most common cause of end-stage renal failure in Western countries
- Other systemic diseases affecting the kidney, often including the glomerulus, include the thrombotic microangiopathies, multi-system autoimmune diseases, including systemic lupus erythematosus and vasculitis, and paraprotein-related renal disease and amyloid.

Tubular injury and interstitial nephritis and tubulo-intersititial disorders

Causes of tubular injury include:

- Ischaemia from prolonged hypoperfusion – acute tubular necrosis
- Toxins, e.g. aminoglycosides, herbal remedies, radiological contrast
- Metabolic, e.g. hypercalcaemia, immunoglobulin light chains
- Crystals, e.g. urate, oxalate
- Rhabdomyolysis (crush injury, status epilepticus, drug overdose.

Causes of interstitial nephritis include:

- Drugs, e.g. NSAIDs, antibiotics
- Infiltrative – lymphoma
- Granulomatous – sarcoidois, tuberculosis
- Infection-related – post infective, pyelonephritic.

CKD is accompanied by tubulo-interstitial atrophy and fibrosis, regardless of the underlying cause. Disorders of the renal vasculature, the glomeruli or urinary drainage all culminate in chronic tubulo-interstitial damage. Drug-induced renal disease can range from renal vasculitis to progressive CKD to ureteric obstruction.

Atherosclerotic renovascular disease (ARVD)

- *Macrovascular renal artery disease or renal artery stenosis (RAS)* is atheromatous in 90% of cases, usually at the renal ostia (within 1 cm of the aorto-renal junction) and because the juxtaglomerular apparatus perceives low volume it stimulates hyper-reninaemic hyperaldosteronism. Fibromuscular dysplasia accounts for around 10% of RAS, classically in a distal, 'sausage-string' pattern, usually presenting as hypertension in young patients, most often women, and there is often a successful response after angioplasty. Occasionally a large renal embolism may result from infective endocarditis or cardiac thrombus. Clinical assessment may detect a renal artery bruit (commonly at the epigastrium) and an atrophic kidney (> 1.5 cm disparity) may be seen on ultrasound. Confirmation is by magnetic resonance or computed tomography angiography. RAS lesions are often functionally insignificant. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial showed no benefit of revascularisation for renal function or blood pressure, and consensus reserves intervention for those with severe RAS and AKI or flash pulmonary oedema. Otherwise medical therapy

Box 2.70 **Causes of kidney disease (acute kidney injury (AKI) and chronic kidney disease (CKD))—cont'd**

appears to be as effective. Where hyperaldosteronism is refractory to medical therapy, angioplasty, stents, artery bypass or nephrectomy may be necessary.

- *Microvascular or 'intrarenal' renovascular disease* may be atherosclerotic. There is usually long-standing parenchymal injury rather than reversible ischaemia, reflected in the variability in renal function outcome after revascularisation for renal artery stenosis. Thrombolysis, anticoagulants or invasive procedures shearing endothelial plaques occasionally trigger embolic showers which scatter through the renovascular system. Episodes of cholesterol emboli may be associated with eosinophilia.
- *Renal infarction* may be asymptomatic or induce loin pain with or without haematuria. A high serum lactate is a strong clue.

ARVD is associated with ageing and other risk factors for atheroma and is commonly accompanied by atherosclerotic macrovascular disease elsewhere, such as coronary artery disease, peripheral vascular disease, cerebrovascular disease and aortic aneurysms. It is a leading cause of hypertension (90% of patients), AKI, CKD and heart failure. There is typically severe systolic hypertension that is resistant to medical therapy. AKI may result from ARVD due to severe bilateral RAS, accelerated hypertension, cholesterol embolisation, radiocontrast agents or agents blocking the renin–angiotensin system. CKD is the most common presentation of ARVD. The hypertension causing the ARVD may be more important in pathogenesis than the 'hydraulic' effects of any RAS lesion – whilst ARVD promotes hypertension, chronic inadequately controlled hypertension causes *nephrosclerosis*, which may promote or accelerate CKD. Heart failure with RAS may be experienced as 'flash floods' of pulmonary oedema. There is usually severe hypertension and bilateral RAS.

Other renovascular disease includes kidney involvement in *systemic vasculitides*, *renal artery dissection,* which can cause back pain, and *renal vein thrombosis,* which may occasionally complicate malignancy or nephrotic syndrome.

Post-renal causes

Obstructive (urological) causes include:

- Prostatic hypertrophy
- Renal stone disease (urolithiasis, nephrolithiasis) – many conditions causing kidney, ureteric or bladder stones including metabolic and inherited disorders, anatomical defects and chronic urinary infection; however, most are idiopathic and present with loin or abdominal pain, and macro- or microscopic haematuria
- Transitional cell carcinoma of the bladder obstructing the ureters
- Ovarian and other pelvic masses obstructing the ureters
- Urethral strictures
- Retroperitoneal and radiation fibrosis
- Urinary tract infection, one of the commonest infections in humans, does not usually cause kidney injury unless part of a complicated infection in patients with anatomical or functional abnormalities of the urinary tract, or severe sepsis.

Box 2.71 **Assessment of fluid status**

It is important to try to decide whether a patient is fluid depleted, fluid overloaded or normovolaemic based on the following:

- Blood pressure (high or low, including presence of a postural drop)
- Jugular venous pulse assessment (misleading in cor pulmonale)
- Examination for oedema (peripheral, sacral or pulmonary)
- Daily weight (1 litre = 1 kg) and fluid balance charts.

These are better signs of fluid status than examining skin turgor and mucous membranes (dehydration used to be assessed as: < 3% – no signs, 5% – dry mucous membranes and reduced skin turgor, 10% – sunken eyes, poor capillary return, > 10% – hypotensive, tachycardic).

Metabolic status. Important renal blood tests (Box 2.72) establish haematobiochemical complications that can be life-threatening or clues to the severity of renal failure and its duration. Renal failure also causes platelet dysfunction, which may respond to synthetic antidiuretic hormone (DDAVP / desmopressin).

Patient perspective

Explore his concerns about his wife and establish her needs, assuring him that you can make all necessary arrangements to secure her safety, for example by contacting relatives, the GP or social services.

Box 2.72 **Important blood tests in kidney disease**

- Potassium
- Bicarbonate: ↓ with a high anion gap metabolic acidosis if severe
- Urea and creatinine*: ↑ proportionately
- Calcium: ↓ then normalised +/– ↑ in chronic kidney disease (CKD)
- Phosphate: ↑ in CKD
- Parathyroid hormone: ↑ in CKD
- Haemoglobin: ↓ in CKD due to failure of erythropoietin synthesis
- White cell count: neutrophilia in sepsis; eosinophilia suggests interstitial nephritis
- Blood film: thrombotic microangiopathies

*A rise in urea disproportionately higher than a rise in creatinine may be caused by dehydration, diuretics, gastrointestinal bleeding, high protein intake, catabolic states such as stress, starvation and steroids, or tetracyclines. A disproportionate creatinine rise occurs in rhabdomyolysis, in which myoglobin released from damaged muscle in severe crush injury, peripheral ischaemia or infarction 'clogs' renal tubules. There is usually other evidence of cell lysis such as raised potassium, phosphate and creatine kinase.

Past medical history

The history of hypertension probably explains his CKD and obstruction from prostatic enlargement the acute presentation.

Drug and allergy history

The angiotensin-converting enzyme (ACE) inhibitor and bendroflumethiazide are now contributing to the mischief and must be stopped.

Family history

It is always important to ask about hereditary kidney disease, notably polycystic kidney disease, although it is unlikely here.

Social history

Establish more details about the care his wife needs and, if necessary, invoke the help of a social worker.

Discussion

What investigations are important in newly detected renal failure?

Tests aim to cause, determine whether acute or chronic, assess severity (Table 2.54) and monitor progress.

Urinalysis

Urinalysis can provide very helpful information in AKI:

- Positive protein values of 3+ and 4+ on reagent strip testing suggest intrinsic glomerular disease.
- A reagent strip positive for blood suggests the presence of red blood cells (> 5 per high-power field). Although red cell morphology may not be particularly useful the observation of large numbers of red cells in the presence of proteinuria suggests a glomerular aetiology for AKI, suspicion strengthened by the finding of red cell casts on a freshly collected sample of urine (this is rarely performed in the UK). Haematuria may also be found in lower urinary tract pathology including tumours, calculi and infection, and in severe renal ischaemia. Characteristically myoglobinuria will cause a positive reagent strip reaction for haematuria without evidence of red cells on urine microscopy.
- Increased numbers of white cells (> 5 per high-power field) are non-specific but found commonly with infection, acute interstitial nephritis, and glomerulonephritis. Eosinophiluria is not a specific test for interstitial nephritis but has value in ruling out the disease.
- Urine microscopy can be informative in particular cases of poisoning, e.g. oxalate crystalluria in ethylene glycol poisoning, urate crystalluria in tumour lysis syndrome, and crystalluria from drugs causing AKI such as sulphonamides, acyclovir,

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ The most likely problem is obstruction on a background of chronic kidney disease with hypertension a significant contributor to the latter.
- ◆ Urgent management includes treatment of hyperkalaemia and bladder catheterisation, involving a urologist if this proves challenging.
- ◆ A full screen of haematobiochemistry and a renal tract ultrasound are essential.
- ◆ You are of course aware of his wife's needs.

Table 2.54 Acute kidney injury staging system and classification

	Stage	Serum creatinine (SCr)	Urine output
KDIGO staging system	Stage 1	↑ SCr ≥ 1.5–1.9 × baseline reference SCr or ↑ SCr ≥ 26 μmol / l within 48 hours	< 0.5 ml / kg / h ≥ 6 hours
	Stage 2	↑ SC ≥ 2.0–2.9 × baseline reference SCr	< 0.5 ml / kg / h ≥ 12 hours
	Stage 3	↑ SCr ≥ 3.0 × baseline reference SCr or ↑SCr ≥ 44 μmol / l from baseline reference SCr ≥ 354 μmol / l or commenced on renal replacement therapy irrespective of stage	< 0.3 ml / kg / h ≥ 24 hours or anuria ≥ 12 hours
RIFLE classification	Risk	↑ SCr ≥ 1.5 × baseline or ↓ GFR ≥ 25%	< 0.5 ml / kg / h ≥ 6 hours
	Injury	↑ SCr ≥ 2.0 × baseline or ↓ GFR ≥ 50%	< 0.5 ml / kg / h ≥ 12 hours
	Failure	↑ SCr ≥ 3.0 × baseline or ↓ GFR ≥ 75%	< 0.3 ml / kg / h ≥ 24 hours or anuria ≥ 12 hours
	Loss	Complete loss of kidney function > 4 weeks	
	End-stage kidney disease	End-stage kidney disease > 3 months	

GFR, glomerular filtration rate; KDIGO, Kidney Diseases: Improving Global Outcomes.

triamterene, indinavir and cathartics high in phosphates.

Blood tests

These should include 'renal blood tests' (Box 2.72), full blood count and clotting screen, and inflammatory markers. An autoimmune screen (antinuclear antibodies, double-stranded DNA, antineutrophil cytoplasmic antibodies, complement components, anti-glomerular basement membrane antibodies) and paraprotein screen (immunoglobulin levels, serum electrophoresis, urine for light chains/Bence Jones proteins or serum free light chains) may be important. Uric acid concentration and creatine kinase if tissue damage is possible (rhabdomyolysis) may be requested, and a blood film for microangiopathic haemolytic anaemia. Hepatitis B virus/hepatitis C virus and human immunodeficiency virus status are needed if renal replacement therapy is likely.

Electrocardiogram and chest X-ray

These are essential for assessing cardiac disease, metabolically driven electrical disturbances and fluid status.

Renal tract ultrasound

Ultrasound is the gold standard test for diagnosis of upper tract obstruction through the finding of hydronephrosis and/or hydroureter. However, upper urinary tract obstruction may not be initially detected by ultrasound in a patient who is volume depleted. There are other circumstances when ultrasound may not be diagnostic, such as in retroperitoneal fibrosis or early in the course of obstructive disease, in which case additional imaging studies may be considered.

Renal biopsy

Renal biopsy is of fundamental importance in nephrology and transplantation. Using appropriate guidelines for including or excluding patients it is generally safe with the commonest complication being bleeding. The biopsy must be processed and stained for standard haematoxylin and eosin sections as well as for immunohistochemistry and electron microscopy to provide a complete picture of the underlying pathology. Renal biopsy should be considered in patients with normal-sized, unobstructed kidneys where acute tubular necrosis (ATN) causing AKI does not seem likely, and without delay in patients in whom rapidly progressive glomerulonephritis due to vasculitis seems likely.

What do you understand by the term acute tubular necrosis or injury (ATN or ATI)?

ATN (injury rather than necrosis reflects potential reversibility) refers to ischaemic tubular damage that is a consequence of pre-renal AKI. Various mechanisms play a role, including intense renal vasoconstriction, formation of tubular casts and reperfusion injury.

How may pre-kidney AKI be distinguished from established ATN or oliguric AKI?

In pre-renal AKI, the tubules can reabsorb and thus concentrate urine. In ATN, the tubules are damaged and 'everything leaks out'. However, pre-kidney AKI often leads to ATN and results become indeterminate. Various measures have been claimed to aid in the differentiation of AKI including urinary sodium, fractional excretion of sodium, urine osmolality, and urine/plasma creatinine and urea ratios, fractional excretion of urea, freewater clearance and creatinine clearance. All of these have limitations and their specificity and sensitivity in clinical practice often means that a single measurement may be inconclusive except in extreme circumstances. In pre-renal AKI there is increased urinary sodium reabsorption and increased urinary urea reabsorption. This should therefore be reflected by low urine sodium concentrations, low fractional excretion of sodium and low fractional excretion of urea, and increased blood urea–creatinine ratios. Urinary electrolytes should be interpreted with caution, particularly in the elderly (who may already have an impaired concentrating ability), and in patients on diuretics (which increase urinary sodium excretion) or with a salt-losing state. In such patients the fractional excretion of urea may be a more useful index. One clinical situation where measurement of urinary electrolytes may have clinical use is in the diagnosis of hepatorenal syndrome as the cause of AKI in patients with liver disease. The diagnostic criteria for hepatorenal failure include a urine sodium of less than 10 mmol/l (Table 2.55).

What are the management principles in an acute uraemic emergency?

The facts of greatest importance are the urine output and serum creatinine (which has an approximate inverse relationship to urine output in the steady state).

Treat the effects

Both rate of deterioration and severity are proportional to the urgency of this response. Urgent attention may be needed for:

- Serum potassium (Box 2.73)
- Fluid status (Box 2.74)
- Acidosis (give intravenous bicarbonate)
- Encephalopathy from uraemia
- Anaemia (occasionally).

Establish and treat the cause

This depends on the setting, which may be expected, as in septic shock or heart failure, or unexpected. Urinalysis for active sediment with blood is an essential first step in considering vasculitis. Nephrotoxic drugs should be stopped. An urgent renal ultrasound helps to distinguish between three possibilities:

- Obstruction, in which hydronephrosis is invariably present

Box 2.73 Treating hyperkalaemia

There is no absolute level of risk. Rate of change is more important, and chronic rises are better tolerated such that extreme levels up to 8 or 9 mmol / l are sometimes seen (although these should still be treated urgently). Fasting lowers insulin levels and may exacerbate hyperkalaemia in chronic kidney disease. Cardiac arrest is rare under 7 mmol / l but 6.5 mmol / l is dangerous and a level > 6 mmol / l warrants close consideration of treatment.

- Calcium (calcium gluconate) is administered intravenously if there are electrocardiogram changes. This promotes intracellular shift of potassium and is cardioprotective. Tented T waves are usually not life threatening but may progress to immediately life-threatening broadening of QRS complexes and T-wave disappearance and a bizarre electrocardiogram. Calcium should be administered immediately with an immediate venous blood gas to urgently estimate serum potassium.
- Dextrose and insulin (50 mmol 50% dextrose with 10 units of Actrapid intravenously over 15–30 minutes) shifts potassium intracellularly and should also be given with or without electrocardiogram changes.
- Salbutamol 10–20 mg by nebuliser acts similarly but causes tachycardia and agitation and may not be necessary if intravenous treatment can be established quickly.
- Bicarbonate may help and is popular in some renal units.
- These measures are temporary, causing potassium shift, but have no effect on total body potassium and levels can swing upwards again within a few hours. Definitive lowering of potassium requires a diuresis (fluid resuscitation if dehydrated, furosemide if fluid overload) but if oligoanuria persists then haemodialysis may be needed.
- Calcium resonium 1 g t.d.s. orally may sustain safe levels, but evidence is weak. This is more likely where there is tissue damage (e.g. rhabdomyolysis) sustaining the problem.
- Stopping exacerbating drugs (e.g. angiotensin-converting enzyme inhibitors, spironolactone, angiotensin receptor blockers) and a low-potassium diet are essential.

Table 2.55 Features that distinguish pre-renal acute kidney injury (AKI) from acute tubular necrosis (ATN)

	Pre-renal AKI	ATN
Urine concentration	Normal	Dilute
Urine sodium (mmol / l)	< 10 (low)	> 20 (high)
Fractional excretion of sodium (%)	< 1	> 1
Urine osmolality (mOsm / kg water)	> 500 (increased)	< 350 (decreased)
Fractional excretion of urea	Low	High

Box 2.74 Managing fluid status

- Volume status must be optimised urgently. Dopamine is of no value, and there is no specific pharmacological therapy proven to effectively treat acute kidney injury (AKI) secondary to hypoperfusion injury and / or sepsis. A central venous line is seldom needed.
- Prescription of intravenous fluid should follow a careful assessment of volume status, i.e. hypovolaemic, euvolaemic, hypervolaemic. A patient with hypotension, postural hypotension, decreased skin turgor and dry mucous membranes will be dry. A dry patient may develop acute tubular necrosis and need dialysis. The most important principle is to put fluid in and 'fill up the bath', and if too much is put in it can be removed and the 'plug pulled' with loop diuresis. Loop diuresis should otherwise be avoided. A patient with a raised jugular venous pulse and oedema will be overloaded.
- Daily sodium intake in health is between 70 and 100 mmol / day. Following surgery or trauma the body's physiological response is to retain sodium and water. The selection of the type of fluid to be prescribed is important as excessive 0.9% sodium chloride (Na 154 mmol / l, Cl 154 mmol / l) can potentially lead to hyperchloraemic acidosis, sodium, chloride and water overload which contributes to postoperative morbidity and mortality whereas excessive 5% dextrose will increase the risk of hyponatraemia. Fluid replacement prescriptions should be tailored to the needs of the patient. Potassium-containing solutions (Hartmann's and Ringer's lactate) should be used cautiously owing to the potential risk of hyperkalaemia.
- Fluid overload causes oedema, myocardial arrhythmias and heart failure, impaired gas exchange, cholestasis, decreased renal blood flow and glomerular filtration rate, ileus and poor tissue healing. The microvascular response to fluids differs from the macro-haemodynamic response, correction of which does not guarantee tissue perfusion, and AKI occurs commonly with a preserved systolic blood pressure.
- Patients at risk of contrast-induced AKI or AKI secondary to rhabdomyolysis should have a careful assessment of volume status and receive pre-procedure volume expansion with 0.9% sodium chloride or isotonic sodium bicarbonate. Potentially nephrotoxic medications such as non-steroidal anti-inflammatory drugs and aminoglycosides should be withheld. There is insufficient evidence to support routine discontinuation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in stable outpatients. Metformin is not nephrotoxic but is exclusively excreted via the kidneys, and patients on metformin who develop AKI are at risk of lactic acidosis.

- CKD with small smooth kidneys
- Normal kidney appearances, indicating acute intrinsic renal failure; this a situation where a normal result indicates an emergency, and immediate nephrology referral for consideration of a biopsy, especially if there is an active urinary sediment (large kidneys occasionally result from infiltrative causes or renal vein thrombosis).

Obstruction is a common cause of AKI, typically in older men with prostatic disease. A bladder is often palpable but chronic retention is usually painless and patients still pass urine – obstruction may be unilateral or there may be a battle between antegrade and retrograde flow before the battle is lost. Chronic obstruction exerts abnormal pressure on tubules and impairs tubular function and this can lead to increased urine output as sodium and water reabsorption is impaired. Significant diuresis may

Table 2.56 Causes of hypokalaemia and hyperkalaemia

Hypokalaemia			**Hyperkalaemia**	
Redistribution	Alkalosis Catecholamines Insulin β_2-agonists Periodic paralyses Rapid cell growth		**Redistribution or spurious**	Haemolysed sample Sample stored on ice Fist clenching Hyperventilation Inorganic acids Diabetic ketoacidosis Lactic acidosis Hyperkalaemic periodic paralyis Cell lysis, e.g. rhabdomyolysis, haemolysis, tumour lysis, chemotherapy
Total body potassium depletion	Decreased intake, e.g. anorexia		**Total body potassium excess**	Increased intake, e.g. bananas, oranges
	Increased loss	Gastrointestinal: urine $K^+ < 20$ mmol / day;		Retention in renal failure
		Renal: urine $K^+ > 20$ mmol / day		
Aldosterone role	Hyperaldosteronism with hypertension, fluid overload and urine $K^+ > 20$ mmol / day	Primary (renin suppressed), e.g. Conn's syndrome, Cushing's syndrome (cortisol has mineralocorticoid activity before metabolised to cortisone)	**Aldosterone role**	Aldosterone deficiency e.g. Addison's disease (hyper-reninaemic hypoaldosteronsism)
		Secondary, e.g. renal artery stenosis (renin stimulated), genetic syndrome (renin suppressed) – pseudohyperaldosteronsism (Liddle's), glucocorticoid remediable hyperaldosteronism, apparent mineralocorticoid excess (Case 2.14)		
	Aldosterone not primarily involved, with normotension and urine $K^+ < 20$ mmol / day	Acidosis (plasma bicarbonate low) e.g. types 1 or 2 renal tubular acidosis		Aldosterone resistance: congenital, e.g. pseudohypoaldosteronsism; acquired, e.g. angiotensin-converting enzyme inhibitors, potassium-sparing diuretics (spironolactone, amiloride), renal tubular disease (systemic lupus erythematosus, amyloid, diabetes mellitus, obstructive uropathy)
		Alkalosis (plasma bicarbonate high) e.g. diuretics, Bartter's syndrome, Gitelman's syndrome, hypomagnesaemia		

See also Case 2.14, Box 2.41, for disorders of aldosterone; Case 2.31 for renal tubular acidosis.

follow relief of obstruction, requiring large volume fluid replacement.

Establish reversibility

If this is not clear, a nephrologist should be consulted. Errors in managing an acute uraemic emergency include failure to identify the cause, delayed referral if renal function is deteriorating and fiddling with irrelevant issues such as watching urine output without acting.

How would you manage a patient with renal and heart failure who has pulmonary oedema but is hypotensive?

Cardiorenal failure is extremely common, with hypotension from left ventricular failure with or without pulmonary oedema, and renal failure from low cardiac output and often renovascular disease. Such patients are fluid overloaded, but the notion of being 'wet but intravascularly dry' is frequently mooted. Treatment of the situation depends upon the goal. To improve breathing, the patient will need to be dry, aided by loop diuretics, and if creatinine rises from, say, 150 to 210, then that is of course perfectly acceptable. But without respiratory symptoms of overload, adequate fluid replacement to maintain acceptable renal function is preferred. What is absolutely illogical and should not be instituted in combination is fluid replacement and diuretics. Occasionally, pure cor pulmonale without left ventricular failure is the cause. There is no evidence in this situation for augmenting treatment with ACE inhibitors when the position has stabilised.

What are the indications for urgent haemodialysis?

Indications for urgent haemodialysis via a temporary central venous catheter include:

- Life-threatening hyperkalaemia
- Pulmonary oedema in an anuric patient
- Symptomatic uraemia, e.g. nausea, drowsiness
- Severe acidosis (e.g. bicarbonate < 12 mmol/l) if unwell or an additional indication is present
- Serositis (now rare), e.g. pericarditis, pericardial rub, pleuritic.

How is serum potassium concentration regulated and what are the causes of hypokalaemia and hyperkalaemia? (Table 2.56)

Acute changes in potassium concentration are usually the result of redistribution between the extracellular fluid and intracellular fluid. Alkalosis, catecholamines (potassium is often slightly low in patients because of the stress response, which increases sympathetic drive and releases glucocorticoids and mineralocorticoids, e.g. after an acute coronary syndrome) and insulin and β_2-agonists tend to redistribute potassium ions into cells. The hypokalaemic and hyperkalaemic periodic paralyses are the result of redistribution abnormalities. Rapid cell growth (e.g. in the treatment of megaloblastic anaemia) may also cause shift of potassium ions into cells. Chronic regulation of potassium concentration is undertaken by the kidney, in the distal tubule. Potassium disorders may be evaluated with three questions:

- Is redistribution likely?
- Is the kidney involved in the pathogenesis (by measurement of urinary potassium)?
- If the kidney is involved, what is the role of aldosterone?

How would you treat hypokalaemia?

Treatment depends upon duration. Chronic hypokalaemia may be associated with a total body potassium deficit > 100 mmol, which should be replaced orally. Intravenous potassium should not exceed 20 mmol/h. If there is concurrent metabolic acidosis, then hypokalaemia should be treated first.

CASE 2.26 CHRONIC KIDNEY DISEASE

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs May Russell, aged 68 years
>
> Thank you for seeing this lady whose creatinine is 175 μmol/l, haemoglobin 9.9 g/dl, albumin 32 and estimated glomerular filtration rate 24. She is otherwise well but her creatinine was 125 μmol/l 12 months ago and I wonder if she now merits a renal opinion. Her blood pressure is 160/92 mmHg and her total cholesterol is 5 mmol/l. Her myeloma screen is negative. She has proteinuria but no blood, glucose or nitrites on urinalysis.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs May Russell is a 68-year-old woman with chronic kidney disease (CKD). She feels well but has been referred to the hospital for an opinion as to whether further investigations are needed because her kidney function has deteriorated moderately since a year ago. Her past medical history comprises hypertension, angina and a possible transient ischaemic attack; she recently had an episode of transient loss of vision in one eye but did not mention this to her GP. She does not have diabetes. Her medications are aspirin 75 mg, simvastatin 20 mg, perindopril 4 mg and atenolol 50 mg, all daily. She also takes non-prescription ibuprofen for back pain, a problem she has had for 30 years since a road-traffic accident. She smokes 10 cigarettes per day. She is very afraid of ending up on 'dialysis' since her husband died of advanced kidney failure due to prostate disease.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

A similar approach to considering causes to Case 2.25 (Acute kidney injury) should be taken.

Patient perspective

Harness her strong desire to avoid dialysis by emphasising the significant benefits of stopping smoking and explain that there are things you can do to modify her risk, including optimising her blood pressure and cholesterol.

Past medical history

The history of hypertension and cardiovascular disease (CVD) imply likely renovascular disease.

Drug and allergy history

The angiotensin-converting enzyme inhibitor can continue but an alternative to non-steroidal anti-inflammatory drugs should be sought.

Family history

Relevance here is unlikely.

Social history

She should stop smoking because this contributes to her coronary disease, likely renovascular disease and possible carotid atheroma.

SUMMARY BOX – ASSESSMENT AND PLAN

- The cause of her chronic kidney disease is likely to be vascular, particularly with isolated proteinuria, but the situation warrants a screen of blood tests and renal tract ultrasound.
- The drugs, including the angiotensin-converting enzyme inhibitor, should continue, the simvastatin should be increased to its optimal dose of 40 mg and her hypertension control should be optimised with the addition of, for example, a calcium channel blocker.
- Further investigation for possible amaurosis fugax includes a carotid Doppler study and possibly ambulatory electrocardiogram monitoring.

Discussion

Why is CKD important?

CKD is associated with substantial comorbidity including hypertension, CVD, anaemia and renal bone disease. People with it are far more likely to die from CVD than progression to renal failure requiring dialysis or kidney transplantation.

What causes CKD?

There are many causes of CKD, the most common being diabetes mellitus (50%) and hypertension (25–50%). Glomerulonephritis is now a relatively small group.

How is CKD defined and classified and how does this aid management?

CKD is diagnosed if evidence of kidney damage has been present for more than 3 months; it is divided into five stages depending on the glomerular filtration rate (GFR) (Table 2.57). The prevalence of stages 3–5 CKD in the UK is around 10%. Stratifying CKD helps to identify patients in whom metabolic complications are likely to arise (stage 3) and guides preparation for dialysis and transplantation. Patients should not be allowed to 'crash land' to haemodialysis as late referral is associated with poorer outcomes (e.g. central-line complications, sepsis) and higher cost.

What do you understand by the term glomerular filtration rate (GFR)?

The glomerulus is a filter producing a cell-free and protein-free ultrafiltrate of plasma which enters the tubule. GFR is determined by the driving force of hydrostatic pressure from the heart and counteractive forces including Bowman's space hydrostatic pressure, oncotic pressures, filter permeability and surface area. GFR is greatly reduced in inflammatory glomerular disease. Normal GFR is around 125 ml/min (around 150–180 litres of ultrafiltrate daily), most of which is reabsorbed by the tubules. GFR is tightly autoregulated by constriction or dilatation of the afferent or efferent arterioles in response to changes in renal artery perfusion. Measuring GFR is unhelpful in acute kidney injury because of rapidly changing function.

What do the renal tubules do?

Glomerular filtration and tubular transport are the two sequential mechanisms underlying renal function. Renal clearance of a substance refers to its net handling and is the sum of urine concentration × urine flow rate/plasma concentration (ml/min). Most reabsorptive processes occur in the proximal tubule and loop of Henle; the distal tubule and collecting duct are important in determining final urinary excretion of water and solutes. Most tubular transport processes are directly or indirectly coupled to reabsorption of sodium ions. Na^+ ions leave the lumen and passively cross the apical surface of the tubular cell down a concentration or electrochemical gradient via Na^+ channels or transporters and exit across the basolateral membrane via a sodium–potassium ATPase pump (ultimately required for most reabsorptive and secretory processes).

How is GFR derived?

Isotope measurement of GFR is the gold standard measurement of renal function. Since measuring it is cumbersome, GFR is estimated (eGFR) by creatinine clearance, a correlate of GFR determined by either the Modification of Diet in Renal Disease or the Cockroft–Gault formula. eGFR is now calculated on all samples sent for creatinine measurement, and creatinine concentration has an inverse relationship to it.

Why is GFR a better marker of renal function than serum creatinine?

The kidneys have enormous reserve. Mildly elevated creatinine may imply that three-quarters of functioning renal tissue is lost. Because of the reciprocal relationship between GFR and creatinine concentration, a small GFR change close to the normal range will have much less effect on creatinine than a small change when the GFR is markedly reduced. Further, changes in creatinine lag behind changes in GFR. Serum creatinine alone is a poor indicator of the degree of renal failure because it is influenced by muscle mass, age, sex, weight, diet and drugs. An elderly patient with a small body mass index and creatinine of

Table 2.57 Classification and management of chronic kidney disease (CKD)

Stage	GFR ml / min / 1.73 m^2 As a general rule, eGFR is a measure of percentage of overall kidney function		Description	Monitoring	Referral to nephrologist	Management
1	≥ 90		Kidney damage with normal or slightly ↑ GFR	12-monthly	Generally managed in primary care Referral if: Proteinuria Microscopic / macroscopic haematuria (urologist if older, nephrologist if younger) Multi-system disease suspected, e.g. systemic lupus erythematosus Family history, e.g. polycystic kidney disease Uncontrolled hypertension GFR declining rapidly	Diagnosis of cause Renoprotection (usually modification of CVD risk factors) Identification of comorbidity Monitoring for progression
2	60–89		Kidney damage with mild ↓ GFR	12-monthly	As for stage 1	As for stage 1
3	30–59	**3a** 45–59	Moderate ↓ GFR	6-monthly	Referral if: Any of the conditions for stage 1 or 2 above are met eGFR falls by at least 10% per year Anaemia Metabolic disturbance (calcium, phosphate, potassium)	As for above stages (but note that extensive investigation unlikely to be rewarding if stable stage 3, asymptomatic and normal urinalysis) + evaluation and treatment of CKD complications (anaemia, calcium and phosphate abnormalities)
		3b 30–44				
4	15–29		Severe ↓ GFR	3-monthly	Urgent referral, especially if any of the conditions for stage 3 are met, diabetes present, GFR is falling rapidly or there are metabolic disturbances inclusive of a low bicarbonate or a raised parathyroid hormone level	As for above stages + preparation for RRT – likely to be needed in 6–8 months Diet assessment Immunisation – influenza, pneumococcus, hepatitis Correction of acidosis with bicarbonate (contentious) Stop metformin if on it
5	< 15 or dialysis		Established renal failure (replaces the term end-stage renal disease)	3-monthly	Immediate	As for above stages + RRT

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; RRT, renal replacement therapy.

300 might have uraemic symptoms while a young muscular patient with a creatinine of 1000 might not. Creatinine may also exhibit a modest decrease because of haemodilution in rapid fluid resuscitation and increase with trimethoprim.

In addition to GFR, detection of kidney disease typically involves measurement of urinary protein (or albumin) concentration. The use of urinary protein–creatinine (or albumin–creatinine) ratios obviates the need for 24-hour urine collections.

Table 2.58 Proteinuria quantification

	Normal	Microalbuminuria	Non-nephrotic range proteinuria	Nephrotic-range proteinuria
Protein excretion (per 24 hours)	< 150 mg	30–300 mg albumin	150 mg–3.5 g protein	> 3.5 g protein
ACR (mg / mmol)	Not detectable	2.5–30 (men) 3.5–30 (women)		
PCR (mg / mmol)	< 15		15–350	> 350 (predominantly albumin with a high urine ACR)

Approximate equivalents:
Albumin to creatinine ratio (ACR) 30 mg / mmol = protein to creatinine ratio (PCR) 50 mg / mmol = urinary protein excretion 0.5 g / 24 h.
ACR 70 mg / mmol = PCR 100 mg / mmol = urinary protein excretion 1 g / 24 h.

Why is proteinuria important?

Proteinuria is:

- A marker of renal disease and of progression of renal disease
- A predictor and risk factor of CVD.

The importance of this is emphasised in the modern CKD classification, and the suffix (p) should be used when denoting the stage of CKD.

Types of proteinuria

Normally low-molecular-weight proteins and albumin filtered from the plasma are reabsorbed in the proximal tubule resulting in a total daily proteinuria of less than 150 mg, of which only around 10 mg is albumin. More than these levels is abnormal, although early renal disease (especially in diabetes) results in low-level albuminuria of 30–300 mg daily known as microalbuminuria, although this is undetectable on most dipstick tests. Proteinuria occurs in a number of states:

- Functional proteinuria (occurs in exercise, fever and heart failure probably due to glomerular haemodynamic changes)
- Overflow proteinuria (increased filtration of low-molecular-weight proteins through a normal glomerular barrier as in light chain proteinuria in myeloma)
- Orthostatic proteinuria (only when upright, not on early morning sample)
- Tubular proteinuria (loss of proteins normally reabsorbed and proteins released by damaged cells)
- Glomerular proteinuria (increased permeability of the glomerular barrier).

Quantification of proteinuria

Quantification of proteinuria has historically been by 24-hour urine collection, but this is inconvenient and thus often inaccurate. Current best practice involves measuring the albumin and/or protein concentration on a spot, ideally early morning, urine sample (Table 2.58). To correct for the effects of urine concentration (hydration state), the albumin or protein concentration is normalised to the creatinine concentration and expressed as the albumin to creatinine ratio (ACR) or protein to creatinine ratio (PCR), respectively expressed as mg albumin or protein/mmol creatinine. An average person excretes 10 mmol of creatinine daily so the ACR and PCR can be multiplied by 10 to give an estimate of the daily albumin or protein loss in mg.

Those with an ACR ≥ 30 and < 70 or a PCR ≥ 50 and < 100 should have confirmation on an early morning sample with a specialist opinion desirable for an ACR ≥ 70 or PCR ≥ 100 unless there is appropriately treated diabetes, or an ACR ≥ 30 or PCR ≥ 50 with haematuria.

Why is early detection of CKD important?

CKD is generally asymptomatic until stage 4, but renal disease is often progressive once the GFR falls below 25% of normal. The haemodynamic changes (including angiotensin II (AII) activity), which sustain renal function initially in surviving nephrons, are ultimately detrimental. People at high risk should be evaluated for markers of CKD (albuminuria, abnormal urine sediment, elevated serum creatinine, decreased GFR) because of the potential to modify disease progression and because of the accelerated CVD associated with CKD.

Which people should be targeted for early detection of CKD?

Those with the following should be offered testing:

- Diabetes
- Hypertension
- CVD (ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease)
- Structural renal or post-renal disease
- Multi-system disease with renal involvement (e.g. systemic lupus erythematosus)
- Family history of stage 5 CKD

Table 2.59 Strategies to slow progression of chronic kidney disease (CKD)

Factors causing progressive decline in renal function	Strategies to slow progression
Persistent activity of underlying cause	Treat cause
Hypertension	Meticulous blood pressure control – the most important intervention to slow progression – with any agent unless proteinuria 120–139 / < 90 mmHg recommended by NICE in CKD (120–129 / < 80 if PCR ≥ 100 or ACR ≥ 70)
Proteinuria, the best predictor of decline	ACE inhibitors or ARBs reduce proteinuria and slow progression of CKD and are first line if: PCR ≥ 50 or ACR ≥ 30 if hypertensive PCR ≥ 100 or ACR ≥ 70 if not hypertensive Diabetes if microalbuminuria – ACR 2.5–30 (men) or 3.5–30 (women) – even if not hypertensive Combining an ACE inhibitor and ARB may be beneficial but may be harmful in minimal proteinuria
Poor glycaemic control	Meticulous glycaemic control as well as blood pressure control
Dyslipidaemia	Use of statins for primary prevention of CVD as for people without CKD Statins for people with CVD
Smoking	Smoking cessation
High phosphate or protein diet	But maintain good nutrition and avoid low-protein diet because malnourishment leads to a poorer outcome with dialysis
Hyperphosphataemia	Phosphate binders
Anaemia (may cause high cardiac output and left ventricular hypertrophy)	Erythropoietin

ACE, angiotensin-converting enzyme; ACR, albumin to creatinine ratio; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; NICE, National Institute for Health and Clinical Excellence; PCR, protein to creatinine ratio.

- Opportunistic haematuria or proteinuria
- Those taking potentially nephrotoxic drugs.

How may acute kidney injury be distinguished from CKD?

Clinical history and knowledge of previous blood tests are most valuable. Calcium and phosphate disturbances may suggest renal osteodystrophy and anaemia may be the result of erythropoietin deficiency, both reflecting CKD. On ultrasonography, small kidneys, thinning of cortices and increased echogenicity favour a diagnosis of CKD.

What strategies can slow the rate of progression of CKD?

Factors causing progressive decline in renal function and strategies to slow progression are outlined in Table 2.59.

How should hypertension be managed in CKD?

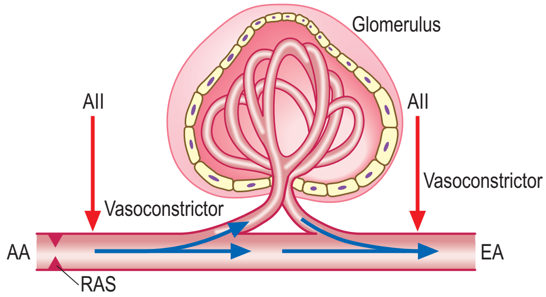
The management of hypertension in renal disease is best understood by classifying patients according to the stage of their CKD. In CKD stages 3 and 4 there is good evidence for slowing the rate of progression of renal disease and reducing cardiovascular morbidity and mortality, and evidence suggests reducing blood pressure to less than 130/80 mmHg. In CKD stage 5, evidence of benefit is more controversial, several studies showing worse outcomes in patients with low blood pressure. In renal transplant recipients additional factors need to be considered such as corticosteroid and calcineurin sparing to reduce hypertension, and blood pressure lowering as in CKD stages 3–4 reduces cardiovascular morbidity and mortality and prolongs graft survival.

What is the rationale for using ACE inhibitors or angiotensin II receptor blockers (ARBs) in diabetic nephropathy?

The strong rationale is discussed in Case 2.23 (Type 2 diabetes).

What is the rationale for using ACE inhibitors or ARBs in non-diabetic nephropathy?

ACE inhibitors slow the progression of non-diabetic nephropathy. In the Ramipril Efficacy in Nephropathy (REIN) studies, ramipril was so effective in slowing the rate of GFR decline in patients with nephrotic-range proteinuria that the trial was stopped early; in patients with 1–3 g/day of proteinuria the median time to established renal failure almost doubled, benefit seen across a wide range of initial GFRs. A meta-analysis by Jafar et al confirmed the benefit and the COOPERATE trial showed that combination of ACE inhibitors and ARBs safely slows the progression of non-diabetic nephropathy.



- ACE inhibitors normally cause dilation of the AA and EA
- In RAS, the AA cannot (functionally*) dilate but the EA can; blood preferentially bypasses the glomerulus

Figure 2.9 Why angiotensin-converting enzyme (ACE) inhibitors are contraindicated in renal artery stenosis (RAS). *The obstruction is really in the trunk artery but the effect is the same – the ratio of supply to EA run-off is reduced and the glomeruli are deprived of blood. AII, angiotensin II; AA, afferent arteriole; EA efferent arteriole; RAS, renal artery stenosis.

How do ACE inhibitors and ARBs delay progression of CKD?

In CKD perfusion of the glomerulus is often maintained by AII-mediated efferent arteriole vasoconstriction. Whilst this is immediately beneficial, it is ultimately destructive as it raises pressure in the glomerulus and predisposes to glomerular sclerosis. Decreasing AII-mediated vasoconstriction with ACE inhibitors or ARBs lowers glomerular pressure and is ultimately beneficial but does cause a reversible rise in serum creatinine or fall in GFR.

Should ACE inhibitors or ARBs be stopped if serum creatinine rises?

Given the above, in CKD creatinine may rise by up to 30% on these treatments but if it subsequently plateaus and serum potassium is within safe limits then ACE inhibitors and ARBs should be continued with close monitoring.

Why might ACE inhibitors or ARBs be dangerous in renal artery stenosis (RAS)? (Fig. 2.9)

Numerous molecules act on the afferent and efferent arterioles in the kidney to maintain GFR. AII is activated by a reduction in renal artery perfusion pressure. This occurs in situations that would cause pre-renal renal failure (hypovolaemia, left ventricular failure, sepsis), which lead to a fall in glomerular hydrostatic pressure, a fall in GFR and in renin release from the juxtaglomerular apparatus. AII promotes aldosterone action and promotes systemic vasoconstriction and renal vasoconstriction (the efferent arteriole is particularly affected and constricts to maintain intraglomerular pressure).

ACE inhibitors and ARBs cause afferent and efferent arteriole vasodilatation. In RAS, the afferent arteriole cannot effectively dilate but the efferent arteriole can. Blood then effectively bypasses the glomerulus.

However, decreased GFR or elevated creatinine do not necessarily occur, even with bilateral RAS, and decreased GFR or elevated creatinine often occur with ACE inhibitors in people without RAS. In any low blood pressure state, GFR becomes AII dependent and thus ACE inhibitor sensitive (RAS is a perceived low-volume state where blood pressure is usually high), ACE inhibitors removing the partially protective effect of AII-mediated efferent arteriolar vasoconstriction.

Furthermore, in CKD of any cause there is an overall drop in GFR because of nephron loss triggering angiotensin-mediated compensatory increased GFR in surviving nephrons; this increase in GFR seldom exceeds 30%.

What do you know about renal metabolic bone disease or osteodystrophy in CKD?

This is summarised in Box 2.75.

Why is CKD associated with accelerated CVD?

CVD is the main cause of death in CKD. Traditional risk factors are common but do not explain an independent very substantial increased risk. In patients with end-stage renal disease requiring dialysis the risk of CVD is approximately 20 times that of the general population. Proteinuria, impaired calcium–phosphate homeostasis, anaemia and inflammation probably contribute. Possible mechanisms for increased vascular calcification include hyperphosphataemia and increased calcium–phosphate product (Ca–PP) – vascular smooth muscle cells exposed to high phosphate enhance osteoblast gene expression; arteriosclerosis and calcification increase pulse wave velocity and left ventricular hypertrophy with reduced coronary flow in diastole.

What do you know about anaemia in CKD?

This is summarised in Box 2.76.

What forms of renal replacement therapy (RRT) are there?

There are haemodialysis, peritoneal dialysis and renal transplantation.

Haemodialysis (Fig. 2.10)

A temporary double-lumen catheter may be inserted into the internal jugular or subclavian vein (the femoral vein is acceptable in an emergency but suboptimal) for emergency haemodialysis. Permanent haemodialysis requires an arteriovenous fistula (AVF) or Gortex graft. An AVF is an anastomosis created surgically between an artery and vein, commonly at the forearm, which dilates over a number of weeks to become suitable for twin-needled

Box 2.75 **Renal metabolic bone disease (MBD)**

Types of renal MBD

Chronic kidney disease (CKD) is associated with various types of MBD, which can start early in CKD (stage 2), and are common in stage 3.

Secondary hyperparathyroidism

In early CKD a slightly raised phosphate (retention) is associated with the potential for mild hypocalcaemia. Decreased 1,25-dihydroxycholecalciferol / vitamin D production by the kidney leads to reduced gut calcium and phosphate absorption and secondary hyperparathyroidism, which normalises serum calcium but increases phosphate. Alkaline phosphatase may be raised. This is, in essence, a high-turnover form of MBD, the drivers being failure of renal bioactivation of vitamin D, phosphate retention and, in some cases, hypocalcaemia.

Osteitis fibrosa cystica refers to the effect of secondary hyperparathyroidism on trabecular bone, with accelerated turnover and fibrosis of marrow; excessive osteoblast and osteoclast activity is driven by parathyroid hormone (PTH) and cytokines. Radiological correlates of hyperparathyroidism are osteopenia and areas of sclerosis ('rugger jersey spine', 'pepper-pot skull') and subperiosteal erosions (starting in the phalanges) and bone cysts.

Tertiary hyperparathyoidism

As CKD progresses, insensitivity of the parathyroids to calcium and skeletal resistance to PTH worsen the situation, ultimately with parathyroid hyperplasia and autonomous PTH secretion – tertiary hyperparathyroidism – provoking hypercalcaemia.

Osteomalacia

Osteomalacia (reduced bone mineralisation) is more readily induced by hypophosphataemia, hypocalcaemia, chronic acidosis and aluminium toxicity.

Mixed renal osteodystrophy

This refers to the combination of increased osteoid (due to hyperparathyroidism) and reduced mineralisation (due to osteomalacia).

Adynamic bone disease

As renal impairment becomes more severe, some patients, particularly under the influence of treatment and especially if diabetic, evolve in a different direction with the development of low-turnover adynamic bone disease associated with relative suppression of the parathyroid glands. This is characterised by reduced trabecular bone formation and resorption, with thinned trabeculae.

Other

Other problems include osteoporosis (especially post-transplantation), dialysis-associated amyloid and metastatic calcification. Uraemic patients develop an internal milieu that favours soft-tissue calcification involving peri-articular tissue, skin and the vasculature. Arterial calcification is associated closely with arterial stiffening, left ventricular disease and increased cardiovascular morbidity and mortality.

Monitoring

Abnormal biochemical parameters of CKD-MBD can be observed relatively early in the progression of CKD, although the rate of change and severity of abnormalities are highly variable among patients and there are no data showing that routine measurement of bone parameters improves outcomes. Current strategies aim to minimise disturbances to skeletal integrity by setting calcium, phosphate, vitamin D and PTH within defined target ranges. It is hoped, but not yet established, that these will also reduce cardiovascular events. Serum calcium, phosphate and PTH concentrations are measured in people with stage 4 or 5 CKD, but not routinely in stages 1–3b. Some recommend measuring alkaline phosphatase and 1,25-dihydroxycholecalciferol / vitamin D.

Treatments

Phosphate

Hyperphosphataemia is one of the commonest biochemical abnormalities through the course of CKD. Hyperphosphataemia contributes to development of low vitamin D levels, hyperparathyroidism, abnormal bone remodelling and vascular calcification. There is a strong association between hyperphosphataemia and mortality in dialysis patients and it is now recognised, from the Framingham Offspring study, that serum phosphate is associated with the risk of cardiovascular disease in the general population. Hyperphosphataemia is generally corrected first of all, and agents include calcium carbonate or calcium acetate (e.g. calcium carbonate or calcium acetate two tablets thrice daily) and lanthanum carbonate. Calcium-based phosphate binders were traditionally first choice, but concerns about increasing the calcium phosphate product have led to the increasing use of lanthanum carbonate and sevelamer. Aluminium toxicity is generally of lesser concern these days and aluminium hydroxide is sometimes used. Serum phosphate in patients with CKD stage 3b–5 should be maintained between 0.9 and 1.5 mmol / l.

Calcium

Serum calcium, adjusted for albumin concentration, in patients with CKD stage 3–5, should be kept within the normal reference range. Calcium load and episodes of hypercalcaemia are associated with a relative increase in vascular calcification and arterial stiffness, although trials of calcium binders have not demonstrated a significant reduction in mortality, despite a reduction in the amount, and progression, of vascular calcification.

1,25-dihydroxycholecalciferol / vitamin D

Vitamin D levels are seldom measured in CKD, and vitamin D replacement tends to be given after phosphate correction if PTH levels are raised. Vitamin D supplementation may be with cholecalciferol or ergocalciferol in stage 1–3b CKD, or 1-alpha-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol) in stage 4–5 CKD (reason more fully explained in Case 2.29 under treatment of hypocalcaemia). However, calcitriol can elevate the serum calcium–phosphate product by increasing gut calcium and phosphate absorption. Calcimimetic agents (e.g. Cinacalcet), which reduce PTH release by direct action on calcium-sensing receptors in the parathyroid glands, may provide future, less calcaemic and less phosphataemic alternatives to calcitriol.

Parathyroid hormone

If vitamin D does not correct PTH levels then parathyroidectomy may need to be considered. Parathroidectomy may also be needed for people not on dialysis in whom serum PTH levels are progressively increasing and remain persistently higher than the upper reference limit for the assay, despite correction of modifiable factors, and this may be the case in tertiary hyperparathyroidism.

Osteoporosis treatment may be given if indicated for the prevention and treatment of osteoporosis in stage 1–3b CKD.

Box 2.76 **Anaemia and chronic kidney disease (CKD)**

Why it occurs

Anaemia is a common complication of CKD, tending to develop once the glomerular filtration rate (GFR) falls below 60 ml / min / 1.73 m^2. Of various contributory factors, the most important is an inappropriately low circulating concentration of erythropoietin (EPO), a hormone largely produced by the peritubular cells of the kidney.

Symptoms

The anaemia causes debilitating symptoms, particularly if severe, including tiredness and lethargy, muscle fatigue, reduced exercise capacity and breathlessness on exertion. There are adverse consequences for a number of physiological systems, particularly those of the heart and brain. High cardiac output and left ventricular hypertrophy are potential complications.

Assessment

Patients with chronic anaemia (haemoglobin (Hb) < 11 g / dl or symptoms) associated with CKD should be investigated. CKD should be considered a possible cause of anaemia when the GFR is < 60. It is more likely to be the cause if the GFR is < 30 (< 45 in diabetics) and no other cause (e.g. blood loss, folic acid or vitamin B12 deficiency) is identified. Measurement of EPO levels should not routinely be used for diagnosis. Laboratory evaluation should include: full blood count with red blood cell indices (mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration); absolute reticulocyte count to assess bone marrow responsiveness (if indicated); serum ferritin to assess iron stores; serum transferrin saturation or reticulocyte Hb content to assess adequacy of iron for erythropoiesis; percentage of hypochromic red blood cells; C-reactive protein to assess inflammation. If the degree of anaemia is proportional to the degree of CKD and is not microcytic, ferritin levels are normal and there are no features of blood loss, seeking a gastrointestinal source of bleeding is unlikely to be necessary. In selected cases, serum B12 and red cell folate concentration, tests for haemolysis, serum and haemoglobin electrophoresis or bone marrow examination may be needed.

Treatment

Synthetic EPO therapy has transformed management of renal anaemia; it induces an increase in haemoglobin concentration and prevents the need for repeated blood transfusions, particularly in dialysis patients. Many patients receiving EPO require supplemental iron, often given intravenously. Several new strategies for stimulating erythropoiesis are currently in development, including prolyl hydroxylase inhibition, EPO gene therapy, and modulation of hepcidin activity.

Treatments for anaemia in CKD include iron, recombinant human EPO and EPO-stimulating agents (ESAs). EPO and ESAs should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function, and to avoid transfusion in patients considered suitable for transplantation, based on local availability. Patients should achieve a Hb level of 10–12 g / dl, although the threshold varies, the aim being to maintain Hb at a level at which patients are unimpeded in their daily activities but below that which may result in excessive thrombotic risk.

Patients should be iron replete and therapy not initiated in the presence of absolute iron deficiency (ferritin < 100 ng / ml). Oral iron will, in general, be sufficient to attain and maintain the Hb above targets in patients not yet requiring dialysis and in those on peritoneal dialysis, whilst most haemodialysis patients require intravenous iron. Intravenous iron (Venofer) 200 mg twice or thrice weekly may be needed. Serum ferritin should not exceed 800 ng / ml.

Once iron is replete, EPO / ESA therapy may be given. The route and frequency of EPO / ESA administration is determined by CKD stage, treatment setting, efficacy, safety and class used; a subcutaneous route is of choice in non-haemodialysis patients, while convenience may favour intravenous administration in haemodialysis patients. Red cell aplasia caused by anti-EPO antibodies and hypertension are possible side effects. Treatments include NeoRecormon (epoetin) 20 IU / kg thrice weekly via a prefilled syringe, Eprex (epoetin) and Aranesp (darbepoetin-α) once weekly. Inadequate response ('resistance') is defined as failure to reach the target Hb level despite a subcutaneous epoetin dose > 300 IU / kg/week (450 IU / kg / week intravenously), or darbepoetin dose > 1.5 μg / kg / week. Hyporesponsive patients who are iron replete should be screened for other common causes of anaemia. Resistance to ESAs may occur in hyperparathyroidism, haematinic deficiency, infection, malignancy or with angiotensin-converting enzyme inhibitors.

dialysis access. By convention, the 'out' line is termed the 'A' line and the 'in' line the 'V' line. The needles point in opposite directions to minimise mixing of outgoing and incoming blood and hence the dialysing of freshly dialysed incoming blood.

From the point of vascular access, blood leaves the body and runs to a pump and thence to the dialyser ('artificial kidney'). The pump is designed not to crush blood cells. In the dialyser, blood enters thousands of semi-permeable microtubules, not dissimilar in diameter to a capillary. Between these microtubules and running in the opposite direction is *dialysis fluid*, against which the blood is dialysed. Dialysis fluid contains concentrations of substances such that an osmotic or ionic gradient is set up from blood to dialysis fluid. Since most patients with CKD are acidotic, dialysis fluid is alkaline and contains bicarbonate, thus allowing correction of acidosis in the blood. However, it is desirable to avoid large ionic shifts. Equally, dialysis fluid contains a low concentration of potassium (1–2 mmol / l) to draw potassium from the blood and usually a low concentration of calcium. Sodium and glucose concentrations are usually normal. Dialysed blood returns to the body via a separate lumen. The *dialysate* is discarded. The transmembrane pressure gradient from blood to dialysis fluid is proportional to the rate and force of the pump. Adjusting the pump settings determines the amount of fluid removed at dialysis. The net amount of fluid removed is called the *ultrafiltrate*. Sometimes, patients are fluid overloaded but metabolically stable. In such cases, pure ultrafiltration, rather than dialysis, is indicated.

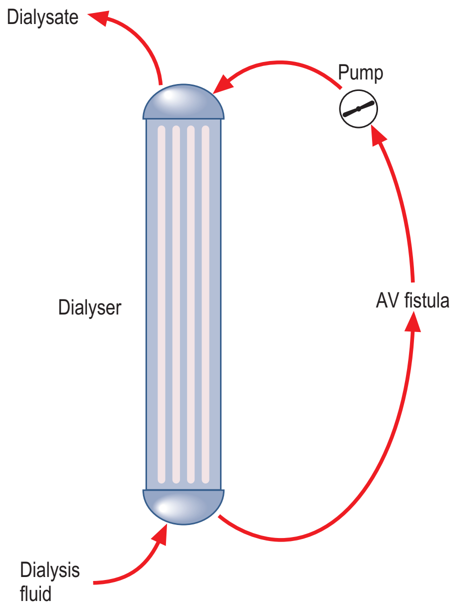


Figure 2.10 Principles of haemodialysis. AV, arteriovenous.

Adjunctive treatments for dialysis patients are as for any patient with CKD.

Complications include access problems, sepsis, haemodynamic instability and β_2-microglobulin accumulation. β_2-microglobulin is a non-dialysed molecule that, over many years, forms amyloid deposits in musculoskeletal tissues. Current definitions of dialysis adequacy, based on urea clearance, need to be broadened to encompass parameters such as β_2-microglobulin clearance, salt and water balance, and phosphate control. Despite major advances in technology, long-term clinical outcomes from haemodialysis are disappointing, even in low-risk patients. More frequent treatments may be necessary to adequately control uraemia and improve survival. Haemodiafiltration improves β_2-microglobulin compared with haemodialysis, and may improve survival.

Peritoneal dialysis

Peritoneal dialysis (PD) is a home-based RRT for patients with end-stage kidney disease (ESKD), offering some degree of autonomy and flexibility of lifestyle. After the placement of a catheter into the peritoneal cavity, the patient is instructed how to perform dialysis exchanges where dialysate is instilled into the peritoneal cavity. These exchanges can either be performed manually (continuous ambulatory or CAPD), or using a machine (automated or APD). During exchange small solutes (such as urea, potassium and creatinine) diffuse from the circulation into the dialysate and are removed when the effluent is drained. On CAPD the standard approach is four exchanges during a 24-hour period using 2 litres of dialysate on each occasion. With APD the dialysis machine performs repeated exchanges overnight and the patient may have additional daytime bags if necessary. Water is removed via the osmotic effect of the glucose in the dialysate, although other osmotic agents can also be used. The most common complication is peritonitis.

Renal transplantation

Renal transplantation is the preferred form of RRT. It restores quality of life and increases longevity for individuals with ESKD. Unfortunately, only 30% of patients who develop ESKD are fit enough to be listed for transplantation, because of excessive comorbidities. The advent of potent immunosuppression has markedly improved 1-year graft survival rates to over 90%. Nevertheless, chronic deterioration of graft function after the first year remains a problem. This is compounded by deterioration in cadaveric donor organ quality, as donors have become progressively older with increasing comorbidity. Kidneys are usually obtained from deceased donors, but the proportion of live donors has substantially increased. Kidney transplant recipients (KTRs) swap one chronic illness for another, with increased risks of vascular disease, neoplasia and infection.

Why is dialysis use increasing?

There is large variation in dialysis prevalence between countries, even across Europe. Dialysis is increasing as a mode of treatment because of an ageing population (now being considered for people in their eighties and nineties) and a result of strategies designed to slow progression of CKD also tending to treat CVD, leading to improved survival from CVD. The context to this is also an increase in diseases that cause CKD, notably diabetes.

When should dialysis be started?

Improved modification of progression of CKD has made predicting the time for dialysis more challenging. Clinical pointers such as appetite, nutrition and cognition are often more helpful than numerical parameters.

When might dialysis be considered inappropriate and 'maximal conservative treatment' appropriate?

The main reason is when patients are dying with, rather than because of, renal failure. Some evidence suggests that, over the age of 75 years with comorbidity, dialysis is of more questionable mortality benefit and that selected patients with high comorbidity live just as long with maximal conservative management as if they had dialysis. However, to withhold RRT from patients with multiple comorbidities without proper appraisal would be ethically questionable. The decision for non-dialysis should be made only after shared decision making between the patient and health-care team. Dialysis is not a true form of RRT; typically it might improve GFR from 5% to 12%, and thus maintains a state of chronic ill health. The aim of RRT is to prolong quantity of life without diminishing quality of remaining years but this is far from always possible. Maximal conservative management is the support of patients with ESKD without resorting to RRT. This support addresses the physical, emotional and spiritual needs until the end of life through a multidisciplinary approach. Medical therapy includes the treatment of underlying renal pathology and other manoeuvres to prolong residual renal function, such as antihypertensive medication and, as renal function declines, treatment of renal anaemia with erythropoietin and optimisation of fluid balance with diuretics.

CASE 2.27 GLOMERULONEPHRITIS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Sam Spider, aged 48 years
>
> Thank you for seeing Mr Spider who has had three episodes of painless macroscopic haematuria recently. His creatinine is mildly elevated at 135 μmol/l and urinalysis continues to show a trace of blood and protein. Otherwise he is a well gentleman. I would value your advice on further investigation.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Sam Spider is a 48-year-old long-haul airline pilot. In the last 3 months he has had three episodes of macroscopic haematuria. On the first occasion he had a mild, concurrent sore throat. All episodes have been without loin or abdominal pain. His GP told him that his blood pressure was very slightly high and that his kidney blood test was slightly raised. He has no other past medical history. He is divorced, does not smoke, drinks occasional alcohol and enjoys keeping active. He is concerned about the possibility of cancer.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Establish the range of symptoms.** Establishing these often leads to consideration of differential diagnoses of each symptom then looking for a diagnosis common to each. Here the combination of symptoms points immediately to the unifying diagnosis of a glomerulonephritis (GN), possibly immunoglobulin A (IgA) nephropathy. It is nevertheless imperative to keep an open mind, consider all possibilities and obtain a reasonably thorough but succinct systematic enquiry.

■ **Consider possible causes of haematuria and the significance of haematuria and proteinuria.** These are described in Table 2.60 and Box 2.77.

Patient perspective

Tell him that you think a form of kidney inflammation, perhaps provoked by the initial sore throat illness, to be

Table 2.60 Causes of haematuria

Transient (usually non-visible) haematuria	Urinary tract infection Exercise
Spurious haematuria	Menstrual Rhabdomyolysis Foods, e.g. beetroot, blackberries, rhubarb Drugs , e.g. doxorubicin, chloroquine, rifampicin Chronic lead or mercury poisoning
'Nephrological' causes	Glomerulonephritis (nephritic syndrome, e.g. IgA nephropathy) Thin basement membrane disease Vasculitis Alport's syndrome Polycystic kidney disease Haemolytic–uraemic syndrome Renal ischaemia / infarct (renal artery thrombosis/renal vein thrombosis) Papillary necrosis Loin pain haematuria syndrome Medullary sponge kidney
'Urological' causes	Cancer (bladder, kidney, prostate, ureter) Calculus disease or nephrolithiasis Cystitis or pyelonephritis Prostatitis or urethritis *Schistosoma haematobium* infection Tuberculosis Radiation cystitis Cyclophosphamide-induced cystitis

Visible haematuria in patients taking antithrombotic drugs reflects underlying pathology in a significant proportion of cases. IgA, immunoglobulin A.

Box 2.77 **Significance of haematuria and proteinuria**

Haematuria

Haematuria may be *visible (macroscopic or gross)* or *non-visible (microscopic or dipstick positive)*. It may be symptomatic or asymptomatic. Chemical urine dipsticks detect haem (intact red cells, free haemoglobin or free myoglobin). A dipstick test for blood is sensitive when performed on fresh voided urine and a score of ≥ 1+ is positive; a trace amount is considered negative. A positive result for haemolysed red blood cells should be treated the same as for non-haemolysed red cells. It is generally not necessary to confirm the dipstick result by microscopy.

Clinically relevant haematuria warranting further assessment

Transient and spurious causes should be excluded before further assessment. Further assessment is warranted with:

- Visible haematuria
- Urinary tract symptoms and non-visible haematuria and a score of ≥ 1+ on a single blood dipstick test
- Asymptomatic non-visible haematuria confirmed on at least two dipstick tests at an interval of 2–3 weeks.

Increased numbers of white cells (> 5 per high-power field) are non-specific but found commonly with infection, acute interstitial nephritis, and glomerulonephritis.

Distinguishing glomerular haematuria from urinary tract haematuria

Glomerular haematuria arises from diseased glomeruli and urinary red cells are typically dysmorphic and form red cell casts in the tubule. Non-glomerular haematuria arises distal to the glomerulus and red cells are more likely to be normal in appearance.

Casts

Casts refers to cylinders of material extruded from the renal tubule:

- The detection of red cell casts is virtually pathognomonic for a glomerular pathology. Casts are fragile, however, and can be very rare or absent even when glomerular disease is present, so testing for them has low sensitivity. The relevance of dysmorphic red cells as indicators of glomerular disease is unclear. The presence of acanthocytes (erythrocytes with ring form blebs) may favour glomerular disease, but other shapes may not necessarily distinguish renal disease from urological disease.
- Granular casts indicate renal disease but are non-specific and common in acute tubular necrosis.
- White cell casts are found in pyogenic conditions.
- Hyaline casts are formed from Tamm Horsfall protein and physiologically secreted in fever and exercise and do not imply disease.

Proteinuria

Proteinuria is a marker of glomerular damage, particularly as the amount of protein increases (low amounts can result from tubular dysfunction); ≥ 2+ is usually glomerular (3+ and 4+ virtually always) and not the result of an asymptomatic urinary infection. The presence of haematuria with proteinuria increases the likelihood that underlying disease is glomerular and is an indication for a referral to a nephrologist.

much more likely than cancer but that your tests will look at all possibilities.

Past medical history

He is previously well, typically the case in many types of GN.

Drug and allergy history

He appears not to be taking any medications but a history taken from anyone with renal disease should ask specifically about non-steroidal anti-inflammatory drugs and non-prescription drugs.

Family history

A family history of renal disease should be sought, especially polycystic kidney disease.

Social history

His occupation is important, and he should be advised to consult with his occupational medical team, who will be familiar with Civil Aviation Authority regulations, to establish his fitness for flying.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ The combination of blood and protein on urinalysis, hypertension and mildly impaired renal function suggests nephritic syndrome, and the synpharyngitic (sore throat concomitant with renal effects) history and episodes of macroscopic haematuria strongly suggest immunoglobulin A nephropathy.
- ◆ The next steps are to arrange examination of urine for casts and dysmorphic red cells, up-to-date renal function and a renal tract ultrasound.
- ◆ The ultrasound occasionally suggests an alternative diagnosis such as renal cell carcinoma; if symptoms suggest ureteric calculi (pain) then an intravenous pyelogram and referral to a urologist might also be indicated.
- ◆ If microscopy reveals casts or dysmorphic red cells or the renal ultrasound and history do not suggest an alternative cause then he should be referred to a nephrologist for early consideration of a renal biopsy to confirm the type of glomerulonephritis.

Discussion

To whom should patients with haematuria be referred?

Urology referral

A urological cause is more likely in patients with either visible haematuria or symptomatic non-visible haematuria, whatever their age, and those with symptomatic non-visible haematuria aged 40 or more. In all these cases, initial referral to urology is important to exclude malignancy. An exception is young adults with cola-coloured (rather than red or pink) urine, particularly after a respiratory tract infection, who are more likely to have acute GN.

Nephrology referral

Patients under 40 with asymptomatic non-visible haematuria are more likely to have renal disease, particularly IgA nephropathy or thin membrane disease. A urology referral is unnecessary and a nephrology opinion is often not required either; a definitive diagnosis requires renal biopsy, and, unless management would be altered, it is hard to justify. In patients under 40, the presence of other risk factors for severe GN does warrant nephrology assessment, namely proteinuria ≥ 0.5 g/day (albumin–creatinine ratio ≥ 30 mg/mmol or protein–creatinine ratio ≥ 50 mg/mmol), an estimated glomerular filtration rate (GFR) < 60 ml/min, or hypertension.

Surveillance

In those referred initially for urological assessment, if no abnormalities are found, nephrological assessment should be obtained if manifestations of kidney disease are present or develop such as deteriorating renal function or proteinuria ≥ 0.5 g/24 hours.

What is glomerular disease?

The glomerular basement membrane (GBM) is the vital barrier between blood and glomerular filtrate. Diseases that damage it generally cause haematuria initially, but as architecture becomes disordered proteinuria becomes an increasing feature. Inflammatory GN most commonly does this, but genetic abnormalities of GBM components are another important mechanism.

How may GN be classified?

GN is confusing because nomenclature attempts to encapsulate aetiology, pathology and clinical presentation. Aetiology descriptions refer to primary causes (unknown but thought to be autoimmune) or secondary causes (associated with autoimmunity, infection, malignancy or metabolic disturbance). Pathological descriptions address glomerular involvement, cell involvement and changes in non-cellular components. Although each clinical presentation can be the result of several types of GN as defined by aetiology or pathology, clinical classification best directs management (Table 2.61).

How prevalent is GN?

The overall incidence and prevalence of GN is unknown because it often causes mild, asymptomatic, unrecognised illness. Population studies have shown that evidence of kidney damage – proteinuria, haematuria, low GFR or combinations of these – affects around 16% of adults in Australia and the USA. Diabetic and hypertensive nephropathy are two major causes, but GN is likely to be the cause in a substantial proportion. Non-visible haematuria is present in about 2.5% of the general population, but it can be as high as 20%, depending on the study population.

What are the common types of GN?

IgA nephropathy is the most common GN, followed by focal and segmental glomerulosclerosis and vasculitis. Defined populations are at increased risk of types of GN. Australian Aboriginals are at increased risk of infection-associated GN after streptococcal throat or skin infections, now rare in developed countries. Chronic infections, notably hepatitis B or C viruses or human immunodeficiency virus, increase the risk of several types of immune-mediated GN.

Which types of GN tend to progress to stage 5 chronic kidney disease (CKD)?

Types that can progress to stage 5 (end-stage) CKD include IgA nephropathy, focal and segmental glomerulosclerosis, rapidly progressive GN with crescents (vasculitis and anti-GBM disease), membranous nephropathy and lupus nephritis. Male sex, hypertension, heavy proteinuria and reduced GFR tend to carry a worse prognosis for most types of GN.

What treatments are there for GN?

Recent understanding of the types of pathology, locations of pathology, important diseases that can result and their clinical presentations, treatments and prognoses are summarised in Table 2.62.

What is anti-GBM disease or Goodpasture's disease?

This is an autoimmune pulmonary–renal syndrome, but not a vasculitis, characterised by anti-GBM antibodies that target renal and pulmonary type IV collagen. Histologically, there is linear GBM immunoglobulin G deposition. This causes rapidly progressive glomerulonephritis and pulmonary haemorrhage, although renal involvement is sometimes the overwhelming problem in isolation. Confusingly, the term Goodpasture's syndrome was used historically for what is now best termed Goodpasture's or anti-GBM disease, while Goodpasture's disease was often reserved for those patients with Alport's syndrome (in

Table 2.61 Classification of glomerulonephritis (GN) by clinical presentation and management principles

Clinical presentation of GN	Management principles
Asymptomatic urinary abnormalities Subnephrotic-range proteinuria and / or non-visible haematuria without renal impairment, oedema or hypertension.	Referral to nephrologist if ≥ 0.5 g protein / 24 hours or glomerular haematuria or abnormal renal function; non-urgent renal biopsy in some cases or close observation in others. Referral to urologist if non-glomerular haematuria for ultrasound, X-ray of kidneys / ureters / bladder, intravenous pyelogram, flexible cystoscopy.
Chronic GN Persistent proteinuria + / – haematuria with slowly progressive renal impairment.	Non-urgent biopsy and treatment to slow progression of chronic kidney disease.
Nephritic syndrome – *the glomerular filter is damaged but inflammation renders it less leaky than normal.* Recent onset of haematuria and proteinuria, renal impairment (often oliguric acute or subacute kidney injury) and salt and water retention causing hypertension.	Usually urgent biopsy to guide management and prognosis.
Nephrotic syndrome – *the glomerular filter is damaged and more leaky than usual. This leads to hypoalbuminuria and oedema.* Nephrotic-range proteinuria (> 3.5 g / 24 hours), hypoalbuminaemia, oedema and hyperlipidaemia, sometimes with predisposition to venous thrombosis and bacterial infection. The selective nature of the proteinuria tends to alter lipoprotein profiles causing loss of natural anticoagulant proteins and immunoglobulin subtypes.	Usually urgent biopsy to guide management and prognosis.
Rapidly progressive GN Progression to renal failure over days to weeks, usually within a nephritic presentation.	Emergency demanding urgent tissue diagnosis (typically extensive crescenteric GN) and treatment.

Table 2.62 Recent understanding of important glomerulonephritides

Location of pathology	Important diseases	Clinical presentation	Treatment and prognosis
Epithelial cell Epithelial cells, in conjunction with the basement membrane, allow filtration of plasma solutes but not proteins and cells. Diseases are typified by flattening or effacement of the foot processes (podocytes) that engage the basement membrane (minimal change disease) and subepithelial / basement membrane immune deposition with spikes and thickening (membranous nephropathy) resulting in disruption of the filtration barrier and proteinuria.	**Minimal change disease** Occasionally associated with Hodgkin's lymphoma or other diseases	Selective proteinuria or nephrotic syndrome, usually in children	Oral prednsiolone 0.5–1 mg / kg daily for 6 weeks then tapered Steroid resistance and relapse more common in adults (cyclophosphamide or ciclosporin)
	Membranous nephropathy Primary due to autoantibodies to a phospholipase A2 receptor Secondary due to malignancy (non-Hogkin's lymphoma, paraneoplasia, carcinoma), drugs (e.g. gold, penicillamine), diabetes, autoimmune disease (lupus, rheumatoid), amyloid or infection (malaria, hepatitis, human immunodeficiency virus)	Non-selective proteinuria or nephrotic syndrome	Oral cyclophosphamide and prednisolone achieves 50% remission rate 30% progress to end stage over 10 years
	Focal and segmental glomerulosclerosis	Variably selective proteinuria or nephrotic syndrome	Nephrotic syndrome or reduced GFR warrant immunosuppression – prednisolone 0.5–1 mg / kg daily for a few months 50% of steroid-resistant cases respond to cyclophosphamide Response reduces progression to end stage by 50% Common reason for renal replacement therapy
	Class V lupus nephritis Probably identical to membranous nephropathy	Nephrotic syndrome	

Table 2.62 Recent understanding of important glomerulonephritides—cont'd

Location of pathology	Important diseases	Clinical presentation	Treatment and prognosis
	Diabetic nephropathy	Nephrotic syndrome	Vigorous control of glycaemia, blood pressure (ACE inhibitor / ARB) and dyslipidaemia
Mesangial cell Mesangial cells are directly exposed to the circulation and deposition of immune complexes is typically seen in diseases such as IgA nephropathy (polymeric IgA deposits) that involve mesangial cells. This results in proliferation (increase in cell number) leading to haematuria, proteinuria and renal impairment.	**IgA nephropathy** Also known as mesangial proliferative GN Identical renal lesions are seen in Henoch–Schönlein purpura, of which IgAN may be the renal limited form	Asymptomatic urinary abnormalities, notably macroscopic haematuria, often synpharyngitic (concurrent) with upper respiratory tract infection or nephritic syndrome	No satisfactory treatment Strict blood pressure control Combined ACE inhibitors and ARB Steroids occasionally helpful Prognosis variable, a substantial proportion progressing to end stage but asymptomatic prevalence unknown
	Class II lupus nephritis	Nephritic syndrome	Treatment not always indicated as prognosis good
	Diabetic nephropathy Nodular and global sclerosis		
Endothelial cell Diseases can result from immune complex deposition, as in infection-associated GN and mesangiocapillary GN, antibody attachment to the basement membrane as in antiglomerular basement membrane disease, or trauma and activation of coagulation as in haemolytic uraemic syndrome. Endothelial cell proliferation and necrosis are accompanied by leucocyte accumulation, and rupture of the basement membrane, crescent formation and disruption of glomerular architecture can develop with nephritic syndrome or rapidly progressive GN.	**Infection-associated GN** Formerly known as diffuse proliferative and exudative endocapillary GN (endocapillary referring to endothelial and mesangial cells)	Nephritic syndrome, tending to be 7–10 days after infection, unlike IgAN, hence its other names: post-infectious GN / post-streptococcal GN. It may be secondary to many other infections, including SBE.	Good prognosis if infection treated
	Mesangiocapillary GN Also known as membranoproliferative GN Due to activation of complement Types 1 (classical pathway, often secondary to hepatitis C or cryoglobulinaemia), 2 (alternative pathway) and 3 (terminal pathway)	Nephritic syndrome	Rituximab (anti-CD20) may be useful in cryoglobulin-associated disease Poor prognosis as tends to cause slowly progressive renal failure, predicted by rate of ↓GFR and degree of proteinuria
	Class III and IV lupus nephritis Proliferative lupus nephritis	Nephritic syndrome	Biopsy essential as type of lupus nephritis not clear clinically but determines therapy Pulsed methylprednisolone then monthly intravenous cyclophosphamide and oral prednisolone for 3–6 months (remission induction) Azathioprine or mycophenolate mofetil and reduced steroid (maintenance)
	Vasculitis	Rapidly progressive GN	Case 2.28 (Vasculitis)
	Antiglomerular basement membrane disease	Rapidly progressive GN	Plasmapheresis, pulsed methylprednisolone followed by oral cyclophosphamide and prednisolone
	Thrombotic microangiopathies Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome		

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GN, glomerulonephritis; GFR, glomerular filtration rate; Ig, immunoglobulin; SBE, subacute bacterial endocarditis.

which type IV collagen is absent) in receipt of a kidney transplant who subsequently developed an anti-GBM response. Nowadays, Goodpasture's or anti-GBM disease refers to patients with anti-GBM antibodies and Goodpasture's syndrome is a rather vague term sometimes, but not ideally, used to denote any pulmonary–renal syndrome.

What is Alport's syndrome?

Mutations in the *COL4A5* (X-linked), *COL4A3* or *COL4A4* (both autosomal recessive) genes cause defective synthesis of the α5-chain collagen type IV with dysfunction of the GBM and sensorineural deafness. Since donor kidneys contain the α5-chain, Alport's syndrome recipients may establish an immune response against them. This is a form of anti-GBM disease and can lead to graft failure.

What is thin basement membrane nephropathy?

This is one of numerous genetic disorders of GBM collagen, and a relatively common form of familial haematuria with a relatively good prognosis.

CASE 2.28 SYSTEMIC VASCULITIS

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr John Silver, aged 65 years

Thank you for seeing this gentleman urgently. He has been breathless for the last 2 weeks and now has recurrent episodes of haemoptysis. His blood tests show a moderate leucocytosis with a neutrophilia, a moderate thrombocytosis, and normochromic–normocytic anaemia. He has raised inflammatory markers with a C-reactive protein of 400. His urinalysis is strongly positive for blood and his serum creatinine is 350 μmol/l.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr John Silver is a 65-year-old man who has been increasingly breathless for the last 2 weeks and over the last 48 hours has been coughing up blood. Over the last 2 months he has felt non-specifically unwell, with unintentional weight loss of around 8 kg and lethargy. His hearing became markedly reduced in his right ear over the course of a few days and he is awaiting an audiology appointment. For around 12 months he has noticed a little nasal stuffiness and on two occasions has been treated for sinusitis and cough. Otherwise he has been a well man apart from mild hypertension, which is being monitored, and gout, for which he takes allopurinol 300 mg daily as prophylaxis. He takes no other medications. He does not have a history of asthma or lung disease. He has never smoked. He lives with his wife, who is wheelchair-dependent with multiple sclerosis but who is otherwise well. He has been told by his doctor that the diagnosis is uncertain, but Mr Silver feels that recurrent chest infections are most likely.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

He has a pulmonary–renal syndrome, possible causes of which are given in Box 2.78.

Patient perspective

Vasculitis is not always easy to explain to patients, and further tests are needed. Explain that this could be infection but that other possibilities that require prompt treatment need to be considered.

Past medical history

The history of nasal stuffiness, and even more importantly the history of sudden hearing loss, is highly suggestive of granulomatosis with polyangiitis.

Box 2.78 **Pulmonary–renal syndromes**

- Antineutrophil cytoplasmic antibody-associated vasculitis (Boxes 2.79 and 2.80)
- Systemic lupus erythematosus
- Anti-glomerular basement membrane disease
- Infection, e.g. pneumonia with acute tubular necrosis, bacterial endocarditis, post-streptococcal glomerulonephritis

Box 2.79 Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Vasculitides associated with ANCAs are systemic autoimmune diseases of unknown cause that affect small to medium-sized blood vessels. They include:

- Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome).

Although relatively rare, they must be diagnosed and treated early because untreated disease may rapidly develop into multiple organ failure and death. With modern treatment, they are no longer fatal but chronic. A large survey of patients with ANCA-associated vasculitis found a lag of 3–12 months between disease onset and diagnosis.

Box 2.80 Clinical manifestations of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Spectrum and overlap of symptoms

- Patients may report different symptoms over time.
- Symptoms of the different ANCA-associated vasculitides overlap, a key feature that should not pose too much practical concern since treatment regimens are similar, but some symptoms are more common in certain diseases.
- Ear, nose and throat problems occur in about 90% of patients with granulomatosis with polyangiitis and in 35% of those with microscopic polyangiitis.
- Lung involvement is more common in granulomatosis with polyangiitis than in microscopic polyangiitis.
- Renal involvement is the most common manifestation of microscopic polyangiitis, affecting the kidney in 90% of cases, and is always ANCA-positive if there is renal involvement with systemic disease but a renal-limited variant may be ANCA-negative.
- Asthma and transient pulmonary infiltrates are common in eosinophilic granulomatosis with polyangiitis; allergic rhinitis and nasal polyps often predate symptoms by many years. Nervous system and cardiac involvement are also common.

Typical presenting symptoms

- Patients typically present with prodromal 'flu-like' symptoms for several weeks or months such as fever, polymyalgia, polyarthralgia, headache, neck-ache, malaise, anorexia, and unintended weight loss. These non-specific symptoms overlap with symptoms of non-vasculitic processes such as infections, or malignancy.
- Though often termed 'systemic' ANCA-associated vasculitis, some patients present with focal vasculitic disease such as rash, cutaneous vasculitis, bloody–purulent rhinitis or scleritis, but with the potential to evolve into systemic vasculitis. A head and neck granulomatosis with polyangiitis and a renal-limited microscopic polyangiitis are not uncommon.

Ear, nose and throat

- Manifestations include persistent hearing loss (sensorineural or conductive – otitis media), otalgia, otorrhoea, recurrent otitis media, nasal stuffiness, (bloody) rhinorrhoea, epistaxis, nasal ulceration and crusting, septal perforation with a saddle nose deformity, sinusitis, hoarseness, stridor, oral ulceration and polychondritis. Subglottic tracheal stenosis affects some patients. Sometimes symptoms may be chronic and insidious and predate systemic disease by months or many years before transforming.
- These are the manifestations with which most granulomatosis with polyangiitis (Wegener's granulomatosis) initially presents.

Lungs

- The airways and lung parenchyma are commonly affected, with cough, haemoptysis, exertional or acute dyspneoa, stridor or wheeze. Alveolar haemorrhage from alveolitis (or sometimes pulmonary granulomatous haemorrhage) is an important cause of mortality. Granulomatous nodules and cavities may be invisible on chest X-ray and seen only on high-resolution computed tomography.

Kidneys

- The kidneys are commonly affected, and urinalysis may identify renal involvement early with detectable haematuria, red cell and other casts, and proteinuria. It is an important cause of morbidity and mortality as renal ANCA-associated vasculitis produces rapidly progressive glomerulonephritis (RPGN) with oliguria, hypertension and renal failure. Renal imaging reveals kidneys of normal size, a situation where normal-looking kidneys constitutes a medical emergency. Biopsy reveals focal necrosis leading to crescents (glomeruli are pressed down into crescents – cresenteric glomerulonephritis – by necrosis) with subsequent monocyte infiltration, glomerular rupture, tubulointerstitial nephritis and sclerosis. Renal disease affects around 20% of all ANCA-associated vasculitis at presentation, but around 80% will develop it.
- RPGN may also be caused by lupus, anti-glomerular basement membrane disease, cryoglubulinaemia and Henoch–Schönlein purpura.

Skin

- About 50% of patients have cutaneous manifestations of disease such as urticarial rash, tender skin nodules or livedo reticularis. The most common skin lesion is leucocytoclastic angiitis, which mostly causes purpura on the lower extremities, sometimes accompanied by focal necrosis and ulceration.

Eyes

- The eyes are commonly affected, presenting as a painful or painless red eye.
- Ocular inflammation includes conjunctivitis, episcleritis, scleritis, exudate at the corneal limbus, sight-threatening 'meltdown'

Box 2.80 **Clinical manifestations of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis—cont'd**

keratitis and uveitis. Scleritis is typical, and untreated can lead to scleral perforation and blindness. Painful proptosis and diplopia may occur in granulomatosis with polyangiitis with orbital granulomata.

- Optic nerve and retinal artery vasculitis are rare, but ANCA-associated vasculitis may affect choroidal vessels.

Nervous system

- Mononeuritis multiplex is seen in 20% of patients, most commonly in eosinophilic granulomatosis with polyangiitis. Cranial neuropathies and central nervous system involvement are very rare.

Other

- Cardiac involvement is not uncommon, aortic valve damage being a feature of granulomatosis with polyangiitis, dilated cardiomyopathy a feature of microscopic polyangiitis and various abnormalities occurring in 30–50% of eosinophilic granulomatosis with polyangiitis.
- Gastrointestinal ANCA-associated vasculitis is rare, and the gut is more often involved in Henoch–Schönlein purpura and cryoglobulinaemia. Inflammatory bowel disease can occur with ANCA-positivity, and limited polyarteritis nodosa can produce bowel perforation.

Drug and allergy history

Allopurinol is potentially nephrotoxic, and, although only a small component of his problems, should at least be dose adjusted.

Family history

Relevance here is unlikely.

Social history

Explore any difficulties that might arise for his wife if he is admitted to hospital.

Discussion

What is vasculitis?

Vasculitis means inflammation of blood vessel walls, the histological triad comprising leucocyte infiltratrion and inflammation, fibrinoid necrosis of the blood vessel wall, and thrombotic vascular occlusion.

What types of vasculitis are there?

There is no indisputable classification, nor are there clear diagnostic criteria. Classification generally starts as primary or secondary, with connective tissue disorders, infection (e.g. viral hepatitis, tuberculosis, human immunodeficiency virus, infective endocarditis), drugs (e.g. biological therapies, hydralazine, propylthiouracil-induced) and malignancy forming large slices of the latter. Primary (systemic) vasculitis may be classified into three main types by vessel type (Table 2.63). A further type, 'other', not in this classification, includes Behçet's disease. Mimics of vasculitis include other pulmonary–renal syndromes and atheroembolism.

Why are vasculitides important to recognise?

Vasculitides are not common (but probably increasing in incidence) and easily missed and different vasculitides affect different age groups – Kawasaki disease affects only children, Henoch–Schönlein purpura usually children, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis only adults and giant cell arteritis older people. Overall, vasculitides are probably less easily recognised in older people but equally common. They are medical emergencies – Kawasaki disease can cause myocardial infarction, ANCA-associated vasculitis can cause life-threatening renal failure and lung haemorrhage, and giant cell arteritis can cause blindness or stroke. Distinguishing the subsets is important because different vasculitides need different treatments. Delayed diagnosis in ANCA-associated vasculitis with a rising creatinine has an adverse effect on outcomes, and 'doctors needed to diagnose' is estimated at around five! Overall survival rates are 83.9% at year 1, 72.9% at year 5 and 63.3% at year 10; without treatment,

SUMMARY BOX – ASSESSMENT AND PLAN

- This is most likely an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with pulmonary haemorrhage and renal failure.
- Malignancy (primary lung cancer or metastatic to lungs) is possible given the weight loss, raised inflammatory markers and history of progressive symptoms over a few months; however, he is a non-smoker, the upper respiratory symptoms are highly suggestive of Wegener's granulomatosis and the active urine sediment with renal failure is typical of ANCA-associated vasculitis.
- Chronic infection such as unresolving pneumonia with an underlying cause or tuberculosis should also be considered.
- His blood tests should be repeated with urgent ANCA testing. Urine should be analysed for casts and dysmorphic red cells. A chest X-ray in ANCA-associated vasculitis may show nodules or other abnormalities. Autoantibody testing for other connective tissue diseases may be undertaken, and complement components C3 and C4 may be low in active immune complex disease (e.g. lupus, cryoglobulinaemia, endocarditis).
- If ANCA-associated vasculitis is likely and infection is not, immunosuppression with high-dose corticosteroids should be started promptly.
- If ANCA-associated vasculitis is subsequently confirmed specialist treatment is needed.

Table 2.63 Classification of vasculitis from the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis, held in 1994

Size of vessel	Typical vessels affected	Diseases
Small-vessel vasculitis (around half of which are ANCA associated)	Arterioles, capillaries and venules but may affect larger vessels	**ANCA associated (with Chapel Hill Consensus Conference criteria)** Wegener's granulomatosis (granulomatous inflammation involving respiratory tract and necrotising vasculitis affecting small- to medium-sized vessels – capillaries, venules, arterioles; necrotising glomerulonephritis common) Microscopic polyangiitis/polyarteritis (necrotising vasculitis with few or no immune deposits, affecting small vessels – capillaries, venules, arterioles; necrotising arteritis of small- and medium-sized arteries may occur; necrotising glomerulonephritis and pulmonary capillaritis common) Churg–Strauss syndrome (eosinophil-rich granulomatous inflammation involving respiratory tract and necrotising vasculitis affecting small- to medium-sized vessels associated with asthma and eosinophilia) (Pauci–immune glomerulonephritis – not in original classification) **Immune complex associated** Henoch-Schönlein purpura Essential cryoglobulinaemic vasculitis Anti-glomerular basement membrane disease Cutaneous leucocytoclastic vasculitis
Medium-sized vessel vasculitis	Main visceral arteries, e.g. renal, hepatic, coronary, mesenteric	Polyartertis nodosa Kawasaki disease (children)
Large vessel vasculitis	Aorta and largest branches directed towards major body regions such as head and neck and extremities	Giant cell arteritis Takayasu's arteritis

ANCA, antineutrophil cytoplasmic antibody.

ANCA-associated vasculitis is invariably fatal, a key natural history study of 56 patients in 1958 finding that average survival was about 5 months; 82% of patients did not survive the first year after diagnosis and more than 90% of patients died within 2 years. The main cause of death was 'uraemia' as a result of rapidly progressive renal failure, and the second most common cause was respiratory failure.

What do you know about the epidemiology of ANCA-associated vasculitis?

The annual incidence of ANCA-associated vasculitis in Europe and Northern America is about 20 per million with a prevalence of around 40 000 in the UK (with point prevalence of 130 / million for granulomatosis with polyangiitis and 47.9 / million for microscopic polyangiitis in the UK in 2008). Disease onset usually occurs at 65–74 years, although it can occur at any age, often slightly younger in granulomatosis with polyangiitis whilst microscopic polyangiitis often peaks in the elderly with a tendency to more severe renal disease, and diagnosis here is often missed. Prevalence is generally higher in men, but women more often develop disease at a younger age. The prevalence of ANCA-associated vasculitis is highest in white people. The incidence of granulomatosis with polyangiitis is higher in northern Europe, whereas that of microscopic polyangiitis is higher in southern Europe.

What causes ANCA-asscociated vasculitis?

Although the exact cause is unknown, ANCA-associated vasculitis is a likely interplay between genetic and environmental factors, although family members or twins of patients with granulomatosis with polyangiitis are rarely reported to have disease manifestations, which goes against a strong genetic predisposition. Among environmental factors implicated are occupational exposure to silica (e.g. farming, construction work), antithyroid and antihypertensive drugs (propylthiouracil and hydralazine), and several microbial agents, particularly *Staphylococcus aureus*. Chronic nasal carriage of *S. aureus* has been associated with a higher incidence of relapse in granulomatosis with polyangiitis and prophylactic treatment with co-trimoxazole reduces the incidence of relapses.

What is the role of ANCA in the pathogenesis of ANCA-associated vasculitis?

All these factors may play a role in the development of ANCAs, which are generally considered pathogenic. A key role for neutrophils in the acute injury to the blood vessel wall is firmly established in ANCA-associated vasculitis. Priming of circulating neutrophils by cytokines, possibly during infection, is thought to underlie local neutrophil accumulation, and priming causes proteinase 3 and myeloperoxidase to be expressed on the neutrophil cell membrane, where it becomes accessible to ANCA. Neutrophils activated by ANCA degranulate, produce reactive oxygen species and release proteolytic enzymes that damage blood vessel walls with highly inflammatory necrosis. Endothelial damage leads to activated endothelium that is prothrombotic and which expresses adhesion molecules that attract more neutrophils and a sustained pro-inflammatory response via monocytes and T cells under the influence of pro-inflammatory cytokines, with ultimate scarring. Because ANCA-associated glomerulonephritis is pauci-immune, with virtually no deposition of complement in renal tissue, it had been assumed that complement played no role in the disease but recent findings support a role.

ANCA correlation with disease

ANCAs may be used to monitor disease activity and indicate risk of relapse, correlating closely with disease activity in many, but not all, patients. The problem with ANCAs as markers of and contributors to disease is that in many patients correlation of ANCAs with disease is poor and in some patients ANCAs are persistently negative.

How is ANCA-associated vasculitis diagnosed?

Diagnosis requires an index of suspicion and usually relies upon the combination of three features (clinically appropriate symptoms, blood tests and specific imaging or histology), best if all three are present, together with exclusion of mimics and observation over time. There is occasionally a 'honeymooon' period after a first relatively limited or mild episode, during which disease may remain suppressed before re-emergence with a vengeance. The reason for this is unclear.

- Blood tests may show leucocytosis, marked thrombocytosis (> 550 × 10^9/l), raised erythrocyte sedimentation rate and C-reactive protein (CRP) values, normochromic–normocytic anaemia (haemoglobin 9–12 g/dl), and a raised serum creatinine. With normal inflammatory markers, platelet counts and haemoglobin levels it is almost always safe to exclude acute systemic vasculitis although the CRP may not be increased in limited disease.
- Higher specificity blood investigations include the eosinophil count in eosinophilic granulomatosis with polyangiitis, and immunological tests – ANCA, antinuclear antibody, rheumatoid factor, anti-glomerular basement membrane antibody, complement components C3/C4 (secondary vasculitis, cryoglobulinaemia), immunoglobulin levels, paraprotein testing and testing for cryoglobulins.
- Urinalysis, including urinary sedimentation, is important to detect haematuria and proteinuria.
- Chest radiography in patients with pulmonary symptoms may detect infiltrates, nodules, cavitations in nodules, stenotic lesions or pleural-based lesions.
- An ANCA assay is indicated in a patient with suspected ANCA-associated vasculitis (Box 2.81). The ANCA test is positive in 90–95% of patients with active generalised granulomatosis with polyangiitis or microscopic polyangiitis before treatment. Two types of assay are generally used: indirect immunofluorescence (IIF) and the enzyme-linked immunosorbent assay (ELISA). IIF is more sensitive (> 95%) but ELISA is more specific (> 99%) and the international standard approach is to use IIF as a screening test and ELISA to confirm positive results. Although the ANCA test is positive in most patients with untreated disease, a negative result does not exclude the diagnosis because 5–10% of patients do not develop ANCA. Further, a negative ANCA test does not exclude other non-ANCA-associated small- and medium-vessel vasculitic syndromes. If there is a high index of suspicion on the basis of clinical findings but the ANCA test is negative, an ANCA assay can be repeated after a few weeks, or more specialist investigation undertaken.
- Computed tomography scanning will provide additional information on the location and nature of lesions identified on chest radiography.
- A diagnosis of ANCA-associated vasculitis is confirmed by specific abnormalities found on tissue biopsies obtained from sites of active disease, such as vasculitis, giant cells, 'geographical necrosis' and granulomas. In granulomatosis with polyangiitis, biopsies from the respiratory tract – mainly nose and sinuses – often do not show more than one of the histopathological hallmarks, and treatment is based especially on typical clinical findings or a positive ANCA test or both; indeed, a renal biopsy for crescenteric glomerulonephritis may be the best biopsy since bronchoscopic biopsy may show granulomata but is often non-specific. Multiple biopsies from active lesions, if possible taken from different organs at different times, increase the chance of establishing a histological diagnosis. When the kidneys are affected, renal biopsies have a higher diagnostic yield, generally showing variable amounts of focal necrotising glomerulonephritis.
- Diagnosis may be much more challenging in those cases where only constitutional symptoms are apparent, with negative ANCA testing, where limited vasculitis remains plausible.

How is ANCA-associated vasculitis treated?

Referral of ANCA-positive patients is usually to a specialist in vasculitis, usually a rheumatologist or nephrologist, or possibly a chest physician. Treatment aims to control disease activity to prevent further damage to organs and to prevent the recurrence of vasculitis. The prognosis for untreated disease is very poor, with a 1-year mortality of around 80%, whilst with treatment survival improved to 70–80% at 5 years. Unsurprisingly, cytotoxic agents that improved survival were for many years used without exposure to clinical trials, but evidence has grown over the last few years, particularly with studies by the European

Box 2.81 **Testing for antineutrophil cytoplasmic antibodies (ANCAs)**

Many conditions can be associated with a positive ANCA, including inflammatory bowel disease, chronic infections (such as tuberculosis), and autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, and ANCA can be induced by several drugs. The presence of cavitating lung lesions and a weakly positive ANCA with raised inflammatory markers may pose diagnostic difficulty, but generally if tuberculosis and infection are ruled out ANCA-associated vasculitis is likely.

Indications for ANCA testing

ANCA testing is indicated when ANCA-associated vasculitis is suspected presenting as an emergency or with unexplained illness lasting more than a few weeks associated with a raised erythrocyte sedimentation rate or C-reactive protein, particularly if more than one organ system is affected, when patients have one or more of the following sets of symptoms:

- *General:* Persistent flu-like illness
- *Ear, nose and throat:* Hearing loss developing over days to weeks; slowly developing nasal stenosis with mid-facial pain and increasing bloody–purulent secretion with crust formation that does not respond to antibiotics (granulomatosis with polyangiitis)
- *Lungs (evidence of acute or chronic destructive upper airway disease or pulmonary inflammatory disease by a variety of clinical symptoms or radiographic abnormalities):* Slowly developing cough and dyspnoea possibly with bloody–purulent sputum, bilateral infiltrates on radiography that do not respond to antibiotics, non-tuberculous cavitating lesions (granulomatosis with polyangiitis) or alveolar haemorrhage (microscopic polyangiitis)
- *Kidneys (evidence of renal inflammatory disease as indicated by an active urine sediment or laboratory parameters indicative of rapidly progressive glomerulonephritis):* Haematuria, proteinuria, hypertension, decreasing renal function (granulomatosis with polyangiitis and microscopic polyangiitis)
- *Skin:* Bursts of small cutaneous vasculitis elements, pyoderma gangrenosum, and oedema
- *Eyes:* Unexplained conjunctivitis combined with general symptoms, uveitis, unilateral proptosis, and paresis of the ocular motor nerves (granulomatosis with polyangiitis).

ANCA testing is also indicated in subglottic stenosis of the trachea manifesting as slowly progressive dyspnoea and retro-orbital mass manifesting as protrusion of the eye bulb and diplopia, although these conditions may be difficult to recognise without specialist tests.

PR3-ANCA (anticytoplasmic cANCA)

- Finely granular staining of the cytoplasm (c-ANCA) is seen on indirect immunofluorescence (IIF); proteinase 3 (PR3) is the antigen in enzyme-linked immunosorbent assays (ELISAs).
- Almost all patients in northern Europe with untreated acute granulomatosis with polyangiitis will be positive.
- Immunomodulatory treatment reduces positivity for PR3-ANCA but positivity increases when treatment is tapered off; re-appearance of PR3-ANCA in non-treated patients may reflect disease activity.

MPO-ANCA (antiperinuclear pANCA)

- Perinuclear staining of the neutrophils (p-ANCA) is seen on IIF; myeloperoxidase (MPO) is the antigen in ELISAs.
- Most patients in northern Europe with untreated acute microscopic polyangiitis and some with granulomatosis with polyangiitis will be positive. In eosinophilic granulomatosis with polyangiitis 50% are pANCA-positive, 25% cANCA-positive and 25% ANCA-negative.
- Immunomodulatory treatment also reduces positivity for MPO-ANCA and it increases when treatment is tapered off, but fluctuations often occur that are not related to disease activity.

Vasculitis Study Group. Rapidly progressive renal failure with an active urine sediment or rapidly progressive haemorrhagic lung disease, with a positive ANCA, are sufficient grounds to institute emergency immunosuppression.

Standard treatment to induce remission

Standard treatment consists of inducing remission with high-dose glucocorticoids (prednisolone 1 mg/kg reduced to 20 mg by week 5 and 10 mg by week 10 but tailored to response or intravenous methylprednisolone 500 mg–1 g daily for 3 days followed by oral prednisolone) and high-dose oral or intravenous pulse cyclophosphamide for 3–6 months, and maintaining remission with azathioprine or methotrexate while glucocorticoids are slowly reduced and withdrawn. Cyclophosphamide can be given in two ways: daily oral cyclophosphamide and pulse cyclophosphamide. In the CYCLOPS trial the group that received pulse cyclophosphamide had significantly less leucopenia than the daily oral group. Trials with intravenous pulse cyclophosphamide as induction therapy have used a minimum 6-month course, but courses of less than 6 months may be appropriate when rapid disease control is obtained. Although methotrexate has been used as induction therapy in place of the potentially more toxic cyclophosphamide for limited or non-severe disease, it is associated with higher relapse rates.

Maintenance treatment

Seventy-five per cent of patients treated with daily oral cyclophosphamide and prednisolone achieve remission by 3 months. By that time, prednisolone is usually reduced to 10–15 mg/day and cyclophosphamide is withdrawn because of the risk of cumulative toxicity and replaced with an alternative immunosuppressant. Patients who do not respond initially to treatment continue with induction treatment for longer and may be considered for second-line treatment. The optimum duration of maintenance treatment is not known and practice differs widely, at least 18–24 months being usual. Alternative maintenance immunosuppressive agents, such as mycophenolate mofetil, might be indicated in individual patients.

Longer term and risk of relapse

In the longer term, regular monitoring is needed (every 3 months at least) to check on disease activity and treatment side effects, and to manage the consequences of irreversible tissue damage, such as renal failure.

With modern treatment ANCA-associated vasculitis has changed from being an imminently life-threatening condition to a chronic condition prone to relapse throughout life. About 50% of treated patients experience one or more relapses by 5 years. Long-term follow-up studies have shown that reducing exposure to cyclophosphamide is associated with a higher risk of late relapse, so a balance is needed between reduced exposure to cyclophosphamide and the increased risk of relapse.

A major relapse may need a return to standard therapy. A minor relapse may warrant an increase in steroid dosage. Indicators of relapse include symptoms, rising inflammatory markers, recurrence of or a rising ANCA titre, active urinary sediment or deteriorating renal function.

Newer therapeutic agents

Rituximab, a monoclonal antibody to CD20 on B cells, which depletes B cells, effectively induces remission in patients with ANCA-associated vasculitis, with a safety profile comparable to standard treatment.

Plasma exchange as adjuvant (adjunctive) to standard treatment for patients with severe renal disease (initial creatinine > 500 μmol/l) is generally safe but with conflicting results.

Specialist otolaryngological management of patients with granulomatosis with polyangiitis

These patients most often have ear, nose and throat (ENT) problems. Initially mid-facial pain, nasal stenosis, bloody–purulent rhinorrhoea, crust formations that may grow into large ‘casts’ of the entire nasal cavities, and hearing loss are important problems, but these symptoms often disappear on treatment. However, sometimes symptoms do not resolve or slowly reappear as treatment is tapered. Most patients with nasal symptoms have a chronic nasal infection with *S. aureus*. Daily nasal lavage with saline is helpful but not curative. Long-term antibiotics can be effective, but infection often reappears when they are tapered. As chronic infection may be difficult to differentiate from smouldering disease, patients may need to be seen by ENT surgeons with experience in vasculitis. Some patients eventually develop destructive midface lesions, such as the saddle nose deformity. Co-trimoxazole prophylaxis is considered in ENT disease as it reduces relapse.

Monitoring

Before each treatment with high-dose cyclophosphamide, platelet and white cell counts, particularly the neutrophil count, must be above the lower limit of normal and liver function must be stable. Creatinine concentrations are needed to make dose adjustments. For daily oral cyclophosphamide, azathioprine, or mycophenolate mofetil, and for weekly methotrexate, routine monitoring of blood counts, liver function, and renal function is important.

Patients are susceptible to infections particularly during induction treatment (usually respiratory or urinary tract infections), and early intervention with antibiotics is needed. With pulse cyclophosphamide, which is routinely followed by antiemetics and oral antifungal treatment, the most vulnerable time for patients is 7–10 days after each pulse. Potential drug interactions are important. For example, patients with granulomatosis with polyangiitis on methotrexate may develop severe neutropenia if treated with standard dose co-trimoxazole; prophylactic low-dose co-trimoxazole (960 mg three times a week) is suggested as standard concomitant treatment with methotrexate.

It is also important to consider the consequences of disease, such as chronic kidney disease, and the effects of treatment. Important side effects of commonly used immunosuppressive agents include: cyclophosphamide: neutropenia, infection, infertility, cancer (especially bladder cancer and leukaemia), haemorrhagic cystitis, alopecia, amenorrhoea; glucocorticoids: osteoporosis, candida, other infections, weight gain, hyperglycaemia, hypertension, Cushingoid appearance, skin atrophy, cataract; azathioprine: nausea, neutropenia, infection, hypersensitivity, cancer, alopecia, cholestasis, thrombocytopenia; methotrexate: nausea, oral ulcers, liver dysfunction, infection, hypertension, leucopenia; mycophenolate mofetil: leucopenia, infection, gastrointestinal tract manifestations, anaemia, thrombocytopenia; rituximab: infections (encephalitis), cancer, anaemia, neutropenia, thrombocytopenia, hypogammaglobulinaemia. There also appears to be an increased incidence of venous thromboembolic events not attributable to classic prothrombotic risk factors. Patients taking immunosuppressive drugs usually require prophylaxis with co-trimoxazole because of an increased risk of acquiring *Pneumocystis jirovecii* pneumonia.

Disease flares

Disease flares are common and patients are encouraged to seek urgent medical attention if they experience a flare, defined as a recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis.

A major flare refers to recurrence, deterioration, or new onset of at least one item on the Birmingham vasculitis activity score, indicating a threat to vital organ function as a result of active vasculitis. Examples include:

- 30% increase of creatinine or 25% decrease of glomerular filtration rate within 3 months
- Evidence of severe pulmonary haemorrhage or granulomata
- Threatened vision (including orbital granuloma and retinal vasculitis)
- Sensorineural deafness
- New multifocal neurological lesions or mononeuritis multiplex
- Gastrointestinal haemorrhage or perforation.

A minor flare refers to recurrence, deterioration, or new onset of at least three other items on the Birmingham vasculitis activity score related to non-vital organs attributable to active vasculitis. Examples include:

- Epistaxis, nasal crusting, lesions on nasal endoscopy
- Conductive deafness
- Rash
- Myalgia, arthralgia, arthritis
- (Epi)scleritis
- Pulmonary symptoms not characteristic of a major relapse.

What is the prognosis in ANCA-associated vasculitis?

Glomerulonephritis results in end-stage renal failure and a need for renal replacement in 20–40% of patients. The risk of death for patients treated with current treatments is still 2.6 times higher than that of age-matched background controls. The increased risk of death is greatest in the first year after diagnosis, when infections and active vasculitis account for most early deaths. Older patients with severe renal impairment have a particularly high risk of dying. Death after the first year is mainly caused by infections, cardiovascular disease and cancer. Patients are at lifelong increased risk of infections and often need treatment with antibiotics.

What is Henoch–Schönlein purpura?

This is a syndrome with four variable features: immunoglobulin A nephropathy (which appears to be a renal limited form of Henoch–Schönlein purpura occurring in around 50%), vasculitic rash in children classically affecting the buttocks but in adults any distribution (100%), arthralgia (75%) and gastrointestinal disturbance (30–40%). In adults, unlike children, bowel wall oedema can be more likely.

What is polyarteritis nodosa?

This is a medium-vessel vasculitis that is ANCA-negative but may share features with ANCA-associated vasculitis. It tends to be overdiagnosed and usually requires the presence of reasonable-sized aneurysms.

What is Takayasu's arteritis?

This is a large-vessel vasculitis, much rarer than giant cell arteritis, predominantly affecting the aorta and main branches. It tends to affect females under the age of 40 and may cause stroke claudication, aortic regurgitation, loss of pulses and blood pressure discrepancy between arms.

What is Behçet's diease?

Behçet's diease remains poorly understood. Pathologically, it is an inflammatory disease, mostly affecting blood vessels, although frank vascular injury is not always apparent and it is not classified as a vasculitis. It probably has an infective or immunological basis in susceptible individuals, and its most constant geographical distribution is along the historical 'Silk Road', being most prevalent in Turkey. Clinical features are highly variable, and may include recurrent painful oral ulceration identical to aphthous ulceration, genital ulceration, gastrointestinal ulceration, skin lesions including pustules and erythema nodosum, uveitis or retinitis, arthritis, headaches or focal neurological symptoms. Venous thromboembolism occurs in around 20%; arterial occlusion is less common. The differential diagnosis includes sarcoidosis, inflammatory bowel disease and Reiter's syndrome and it is usually a diagnosis of exclusion. Corticosteroids may help in managing lesions.

CASE 2.29 HYPERCALCAEMIA

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Jake Marley, aged 72 years
> Thank you for seeing Mr Marley, who has had back pain for a few months and whose blood tests show a corrected serum calcium of 2.9 mmol/l and a normochromic normocytic anaemia. He is previously well and I am concerned about the possibility of myeloma, although his protein electrophoresis shows a moderate polyclonal pattern without a monoclonal band. His renal function is normal. I would appreciate your urgent assessment.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Jake Marley is a 72-year-old man who has been losing weight for around 4 months, and in the last 2 months has developed a gnawing pain in his lower back that is now keeping him awake at night. More recently, he has had night sweats. His past medical history comprises a melanoma excision from his right shoulder area 4 years ago and prostate trouble. He has had a poor urinary stream for a couple of years and his GP told him it was probably the result of an enlarged prostate. He lives with his wife, who herself has osteoporosis and who has been struggling increasingly in the last few weeks to manage him at home. He does not have any lower limb weakness but is very disabled by the pain. He is a smoker of 10 cigarettes per day. He and his wife had thought his back pain might also be the result of osteoporosis.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Explore symptoms of hypercalcaemia.** These include polydipsia, polyuria and pain due to ureteric calculi. 'Moans, stones, bones and groans' (depression, ureteric calculi, bone pain, abdominal pain, dyspepsia) beloved of textbooks are not that common. Severe constipation, confusion or rigidity may occur with calcium levels over 3.0 mmol/l, where the cause is usually neoplastic.

■ **Explore the worrying symptoms.** Weight loss, night sweats and the gnawing back pain are a significant worry and should alert you immediately to the possibility of cancer and prompt a full systematic enquiry. Back pain and urinary symptoms should raise the possibility of cord compression but the absence of lower limb symptoms is at least a little reassuring.

Patient perspective

There is a need to gently expose the possibility of an unwelcome diagnosis, without leaping to malignancy, given that it is not something he has considered. This may be done by expressing your concerns that things may not be as simple as they seem, that there is a wide range of possibilities but that you see a compelling need to investigate things urgently, keeping in mind the possibility of finding something that may not be nice. You could allude to the history of melanoma and say that sometimes there is a link with these sorts of symptoms and a history of melanoma.

Past medical history

The prostate symptoms and the history of melanoma are both potentially highly relevant.

Drug and allergy history

Not relevant here.

Family history

Hypercalcaemia only seldom has a familial basis and this is not a consideration here.

Social history

You should be concerned that he is becoming immobilised by pain and that his wife is struggling.

SUMMARY BOX – ASSESSMENT AND PLAN

- Primary hyperparathyroidism (PHPT) and malignancy are the commonest causes of hypercalcaemia. Malignancy can cause hypercalcaemia by bone metastases or by release of parathyroid hormone (PTH)-related peptide (PTH-rp) by the tumour directly.
- PHPT is more common in outpatient settings and malignancy is more common in patients who have been admitted to hospital.
- Hypercalcaemia should usually be confirmed on two separate samples before further investigation.
- The next step is usually to perform a PTH assay. This is raised in PHPT, and often normal or suppressed in hypercalcaemia linked to malignancy. PTH-rp is not detected by the standard PTH assay and does not influence standard PTH levels. However, a PTH assay is not always needed in patients where hypercalcaemia is very likely to be a manifestation of malignancy.
- This patient very likely has malignancy, and bone metastases seem likely, either from prostate or from melanoma. Bone metastases from melanoma can appear lytic, behaving not dissimilarly to myeloma. Examination should include prostate examination and further investigations should include a full screen of haematobiochemistry, inflammatory markers and prostate-specific antigen, chest X-ray, thoracolumbar spine X-ray and a bone scan. Urinary light chains should be sought for completeness if considering myeloma, but the polyclonal electrophoresis and a more plausible sequence of pathological events make myeloma less likely. If these tests do not confirm a cause, a PTH assay and PTH-rp assay may be warranted, and a computed tomography scan of thorax, abdomen and pelvis might detect carcinoma or lymphoma.
- Hospital admission may be the most effective way of managing the overall situation – a need for urgent investigation, to manage his pain and to provide respite for his wife.

Discussion

What are the causes of hypercalcaemia?

These are listed in Box 2.82.

Primary hyperparathyroidism (PHPT) is usually due to a solitary adenoma but occasionally multiple adenomas or hyperplasia; carcinoma is exceptionally rare. It is occasionally associated with multiple endocrine neoplasia (MEN) syndromes. In MEN1, PHPT is usual, often with pancreatic tumours and sometimes with pituitary adenomas. In MEN2 medullary thyroid cancer and phaeochromocytoma are more likely than PHPT.

What is familial hypocalciuric hypercalcaemia (FHH)?

This is a rare autosomal dominant condition with inactivating mutations in calcium-sensing receptor genes. Parathyroid cells are mildly resistant to calcium and there is reduced ability for the kidneys to upregulate calcium

Box 2.82 Causes of hypercalcaemia

- Primary hyperparathyroidism
- Malignancy due to bone metastases or parathyroid hormone-related peptide produced by tumour
- Myeloma
- Tertiary hyperparathyroidism in kidney disease
- Thyrotoxicosis
- Addison's disease
- Excess calcium ingestion
- Milk-alkali syndrome
- Drugs, e.g. thiazides, lithium
- Paget's disease (if immobilisation)
- Familial hypocalciuric hypercalcaemia

excretion. Serum calcium is modestly elevated with an inappropriately normal parathyroid hormone (PTH) level and this can mimic PHPT. The calcium–creatinine clearance ratio can help distinguish FHH from PHPT, as can 24-hour urinary calcium levels.

How does PHPT present?

The traditional 'bones, stones, abdominal groans and psychiatric moans' from hypercalcaemia is no longer commonplace, and skeletal complications (osteitis fibrosa cystica) are now present in < 5% of presenting patients and renal stones (nephrocalcinosis and nephrolithiasis) in 15–20%. PHPT is most frequently found coincidentally on biochemical testing – hypercalcaemia with inappropriately high PTH secretion. Few patients volunteer symptoms or have evidence of end-organ damage, but may complain of non-specific symptoms such as fatigue, weakness, poor memory and difficulty concentrating.

How is PHPT managed?

Surgery is the only cure for PHPT and is very effective. Minimally invasive surgery is often possible for patients where there is concordant nuclear medicine (SestaMIBI SPECT scan or thallium subtraction scan) and ultrasound evidence of an isolated adenoma. Otherwise, subtotal or total parathyroidectomy may be needed. Tests to establish disease extent may also include computed tomography or magnetic resonance imaging or selective venous sampling.

Surgery reduces the risk of renal stones in symptomatic patients, causes rapid and sustained increases in bone mineral density (BMD) and reduces fracture risk. It is therefore appropriate in symptomatic PHPT and where there is evidence of end-organ disease but there remains controversy where there are no clinical features.

Complications of surgery include hypoparathyroidism, which is common but which usually resolves quickly; oral calcium and 1α-hydroxyvitamin D are needed. More severe hypocalcaemia may result from 'hungry bones' in patients with pre-existing bone disease, and may require intravenous calcium. Permanent hypoparathyroidism is rare.

Box 2.83 Guidelines for surgery in primary hyperparathyroidism

Symptomatic

- Renal stones
- Polyuria / polydipsia
- Pancreatitis
- Neuropsychiatric disorder
- Florid bone disease, e.g. osteitis fibrosa cystica
- Previous hypercalcaemic crisis

Asymptomatic

- Age < 50
- Serum calcium > 0.25 mmol / l above upper limit of normal (~> 2.9 mmol / l)
- Estimated glomerular filtration rate reduced to < 60 ml / min
- Bone mineral density (by dual-energy X-ray absorption) T-score < 2.5 at any site, and / or fragility fracture
- Medical follow-up undesired or impractical

The most widely used consensus guidelines come from the National Institutes for Health (Box 2.83).

Patients who do not fulfil guidelines for surgery are offered structured conservative follow-up (review of symptoms 6–12 monthly, serum calcium 6–12 monthly, renal function 12 monthly, bone density every 2 years; previous recommendations for 24-hour urinary calcium and imaging for renal stones are not now recommended) and advice on hydration status and symptoms.

What are the pros and cons of treating mild PHPT conservatively?

The potential benefits of cure need to be balanced against the risks of surgery.

Factors which may favour a conservative approach include old age, short life expectancy, high operative risk, patient preference, low fracture risk, low risk of worsening renal function and low risk of neuropsychiatric disease. Factors which may favour surgery include the opposites of these.

There is growing concern that PHPT is an independent risk factor for cardiovascular morbidity and mortality and perhaps malignancy.

Cardiovascular risk with mild PHPT

PHPT in its most severe form is associated with cardiac and valvular calcification. There appears to be a significant increase in cardiovascular mortality in moderate to severe (symptomatic and / or calcium > 3.0 mmol / l) PHPT that reduces after surgery. Both serum calcium and PTH are independent risk factors for coronary artery disease in the general population (so not necessarily generalisable to

PHPT) and whether mild, asymptomatic PHPT is a cardiovascular risk factor is not clear but it may be a prominent risk factor for arterial stiffness and hypertension and left ventricular hypertrophy.

Cancer with mild PHPT

An increased risk of cancers has been reported in PHPT and is estimated to be approximately double that expected. A small contribution to this might be from endocrine tumour syndromes such as MEN that have PHPT as a feature. There may also be biases in studies since malignancy is often a prompt for biochemical testing during which incidental PHPT might be detected and patients with hypercalcaemia detected unexpectedly are likely to receive assessment for malignancy.

What medical treatments are possible in mild asymptomatic PHPT?

Adequate fluid replacement is vital. Steroids may be useful in suppressing hypercalcaemia in malignancy. In PHPT, calcium tends to correct only with surgery.

Bisphosphonates

Oral bisphosphonates do not provoke long-term reductions in serum calcium in patients with PHPT but can be considered for the associated bone disease. Alendronate is the most extensively studied bisphosphonate in PHPT, reducing bone turnover and increasing BMD but there are no data on reduced fracture risk.

Cinacalcet

The central regulator of PTH secretion is extracellular ionised calcium, which acts via the calcium-sensing receptor (CaSR). Stimulation of the CaSR results in inhibition of PTH gene transcription, reduced PTH secretion and reduced parathyroid cell proliferation. Molecular characterisation of the CaSR has allowed development of agents known as calcimimetics that modify the CaSR without having true calcium effects peripherally. The calcimimetic cinacalcet is useful in primary and secondary hyperparathyroidism, producing rapid and sustained reductions in serum calcium. Increased BMD has not been observed. In the UK cinacalcet is licensed for use in PHPT in patients in whom surgery is inappropriate and is potentially valuable with life-threatening hypercalcaemia associated with PHPT. The absence of hard clinical endpoint data and cost mean that cinacalcet cannot currently be advocated as an alternative to surgery.

What are the possible endocrine manifestations of malignancy?

Common hormones produced by tumours are listed in Table 2.64.

Rarer hormones produced by tumours include renin (renal cell cancer), insulin-like growth factors and vasoactive intestinal peptide (VIPoma).

Table 2.64 Hormones produced by tumours

Parathyroid hormone-related peptide	Breast cancer Squamous cell cancer, e.g. lung, head and neck, oesophagus Adenocarcinoma of lung Other solid tumours, e.g. ovary, bladder Lymphoma Phaeochromocytoma Myeloma
Antidiuretic hormone (ADH; in syndrome of inappropriate ADH excess)	Small-cell lung cancer Cancer of duodenum, pancreas, colon, genitourinary tract Squamous cell cancer of head and neck Lymphoma Carcinoid tumour
Adrenocorticotropic hormone	Lung cancer, especially small cell Pancreatic cancer Thymus cancer Bronchial carcinoid Many others less commonly

What are secondary and tertiary hyperparathyroidism?

Secondary hyperparathyroidism corrects the tendency to hypocalcaemia in chronic kidney disease, causing calcium and phosphate release from bone. Phosphate cannot be cleared and so accumulates, creating a vicious cycle. In tertiary hyperparathyroidism the PTH rise is inappropriately large, overshooting its original purpose because the parathyroids have been chronically stimulated and have become autonomous secretors, leading to hypercalcaemia.

What happens to serum levels of alkaline phosphatase in hyperparathyroidism?

These increase, because bone turnover is increased.

How is serum calcium normally regulated?

Normal serum calcium is around 2.10–2.60 mmol/l and regulated by the actions of PTH and vitamin D.

Parathyroid hormone (PTH)

PTH is normally suppressed by hypercalcaemia, and activated by hypocalcaemia. Calcitonin (from thyroid C cells) essentially opposes the actions of PTH. PTH normally prevents hypocalcaemia by:

- Promoting tubular reabsorption of calcium (and excretion of phosphate) and activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (also known as 1,25-dihydroxycholecalciferol or calcitriol) in the kidney
- Inducing osteoclast activity in bone, thereby increasing serum calcium and phosphate
- Promoting gastrointestinal absorption of calcium.

Vitamin D

Vitamin D is produced in the skin by the action of ultraviolet light on 7-dehydrocholesterol and absorbed from the gut; it is converted in the liver to 25-hydroxyvitamin D and then in the kidney to its most active form 1,25-dihydroxyvitamin D, which promotes gut absorption of calcium, enhances tubular resorption of calcium and excretion of phosphate and increases bone mineralisation.

What are the causes of hypocalcaemia?

Causes are shown in Table 2.65.

How may hypocalcaemia present?

Extracellular calcium concentrations are vital for neuromuscular function and classic symptoms of hypocalcaemia are those of neuromuscular excitability – muscle twitching or spasm, or sensory symptoms. Carpopedal spasm is characteristic but severe cases may progress to tetany, seizures and arrhythmias. Neuromuscular excitability may be evoked by Chvostek's sign or Trousseau's sign. Clinical features of hypocalcaemia are outlined in Table 2.66.

The development of symptoms or signs of hypocalcaemia tends to reflect both absolute levels and how rapidly it falls – abrupt falls may produce significant neuromuscular symptoms and threaten life; long-standing hypocalcaemia may present with neuropsychiatric symptoms, cataracts and occasionally raised intracranial pressure. Chronic hypocalcaemia may be asymptomatic.

What is 'simple' vitamin D deficiency and how does it differ from vitamin D deficiency with secondary hyperparathyroidism?

Biochemical changes in various types of vitamin D deficiency are outlined in Table 2.67.

Table 2.65 Causes of hypocalcaemia

Cause		**Serum levels**				**Comment**
		PTH	**25-hydroxy-vitamin D**	**Alkaline phosphatase**	**Phosphate**	
Vitamin D deficiency	Limited ultraviolet exposure or dietary deficiency	High	Low	Normal/high	Low	Common Dietary deficiency less common than limited ultraviolet exposure, but vitamin D requirements increase in pregnancy
	Malabsorption	High	Low	Normal/high	Low	Small bowel disease (e.g. coeliac disease) impairs calcium and vitamin D absorption
	Renal disease	High	Low	Normal/high	High	Common Reduced activation of vitamin D
	Anti-epileptic drugs inducing enzymes that increase vitamin D metabolism	High	Low	Normal/high	High	Common Reduced activation of vitamin D Liver disease can also cause vitamin D deficiency with failure of conversion to 25-hydroxy-vitamin D
	Vitamin D resistance	High	Normal	Normal	High	Rare
Hypopara-thyroidism	Hypoparathyroidism after thyroid or parathyroid surgery (rarely due to infiltration – haemochromatosis, Wilson's disease, metastases)	Low	Normal	Normal	High	Common Parathyroidectomy for hyperparathyroidism may also induce hungry bone syndrome
	Autoimmune disease	Low	Normal	Normal	High	Rare e.g. autoimmune polyglandular syndrome type 1
	PTH resistance (pseudohypopara-thyroidism)	High	Normal	Normal	High	Rare

Table 2.65 Causes of hypocalcaemia—cont'd

Cause		**Serum levels**				**Comment**
		PTH	**25-hydroxy-vitamin D**	**Alkaline phosphatase**	**Phosphate**	
Other	Hypomagnesaemia	Normal / low	Normal	Normal	Normal/low	Common Magnesium necessary for PTH release
	Autosomal dominant hypocalcaemia	Normal	Normal	Normal	Normal	Rare Due to a mutation in the *CasR* gene, which normally negatively regulates PTH secretion from the parathyroid gland and calcium resorption in the kidney; the mutation actually lowers the threshold for the action of CaSR, so that PTH is more readily suppressed and calcium more readily excreted by the kidney
	Sclerotic metastases	High	Normal	High	Low	Rare
	Critical illness					Very common in intensive care
	Post bisphosphonate treatment					Bisphosphonates block bone resorption
	Infusion of phosphate or calcium chelator, e.g. citrate with massive blood transfusion					

CaSR, calcium-sensing receptor; PTH, parathyroid hormone.

Table 2.66 Clinical features of hypocalcaemia

Paraesthesia	Extremities and circumorally
Chvostek's sign	Twitching of circumoral muscles on gentle tapping of facial nerve over parotid gland (false negatives and false positives common, occurring in 10% of normal people)
Trousseau's sign	Carpal spasm on inflation of the blood pressure cuff (more sensitive and specific than Chvostek's sign), which can be very painful
Muscle cramps	Often of legs Carpopedal spasm (tetany) Most threateningly respiratory muscle spasm
Neurological	Altered behaviour Seizures
Cardiac	Prolonged QT interval and risk of ventricular arrhythmias

What are the clinical manifestations of vitamin D deficiency?

Vitamin D deficiency causes secondary hyperparathyroidism and precipitates or exacerbates osteopenia and osteoporosis. Raised PTH levels induce phosphaturia and hypophosphataemia; this causes a mineralisation defect of the osteoid (osteomalacia), which unlike osteoporosis can cause non-specific aches and pains in bones and muscles, and severe proximal myopathy and impaired balance. Alkaline phosphatase levels are often elevated in osteomalacia.

What is pseudohypoparathyroidism?

This refers to end-organ resistance to PTH (PTH fails to activate its signalling pathways), resulting in biochemical changes mirroring hypoparathyroidism, with hypocalcaemia and hyperphosphataemia, but PTH levels are raised. There are various forms of inheritance, one of these is the result of mutations in the *GNAS* gene, which encodes a signalling effector of PTH action; the clinical features may include short stature, obesity, short fourth and fifth metacarpals, learning difficulties and basal ganglia calcification, a syndrome known as Albright's hereditary osteodystrophy.

What is pseudopseudohypoparathyroidism?

This refers to the phenotype of pseudohypoparathyroidism, but with normal biochemistry. PTH action on the kidney is normal but because of impaired PTH action on bone there are features of Albright's hereditary osteodystrophy.

Table 2.67 Biochemical changes in vitamin D deficiency

	Vitamin D level	Serum calcium	PTH level
'Simple' vitamin D deficiency	Low	Normal	Normal
Vitamin D deficiency with secondary hyperparathyroidism	Low	Low / normal	Raised (secondary, compensatory hyperparathyroidism)
Primary hyperparathyroidism masked by coexistent vitamin D deficiency	Low	Normal	Raised

PTH, parathyroid hormone.

How might you approach assessing for causes of hypocalcaemia?

A general approach to investigation for causes starts with a PTH level:

- Raised PTH suggests renal disease if renal failure is evident, but otherwise should prompt assay of 25-hydroxyvitamin D, the latter low in vitamin D deficiency and normal in pseudohypoparathyroism
- Low or normal PTH suggests hypoparathyroidism provided magnesium levels are normal.

What levels of calcium are worrying?

Serum calcium must be interpreted in relation to serum albumin. Serum calcium exists in its ionised form (the biologically relevant form, normally constituting around 50% of serum calcium) and bound to albumin, and since many medical conditions lower albumin concentrations serum calcium must be corrected to a reference albumin of 40 g/l – for each 1g/l of albumin above or below this value calcium is adjusted by decreasing or increasing by 0.02 mmol/l, e.g. a serum calcium of 2.0 mmol/l with an albumin of 30 g/l would be corrected to 2.2 mmol/l. This calculation is not always reliable (in critical illness or in inappropriately low situations such as contamination of blood samples by EDTA or post certain gadolinium contrast agents) and ionised levels can be checked directly.

How should hypocalcaemia be treated?

Acute hypocalcaemia

Symptomatic hypocalcaemia or asymptomatic people with a corrected serum calcium under 1.9 mmol/l may be at risk of life-threatening complications and treatment with calcium gluconate is the preferred intravenous calcium since calcium chloride irritates veins. One or two 10 ml ampoules of 10% calcium gluconate diluted in 50–100 ml of 5% dextrose may be infused slowly over 10 minutes with cardiac monitoring; treatment may be repeated until symptoms clear, but relief may be temporary without ongoing infusion of more dilute calcium, e.g. 10 ampoules of 10% calcium gluconate in 1 litre of 5% dextrose or 0.9% saline at an initial rate of 50 ml/h, aiming for a calcium level at the lower end of the reference range. Oral calcium should be given concurrently, as calcitriol if PTH is deficient. Where hypomagnesaemia is the cause of hypocalcaemia, magnesium replacement is the key to restoration of normocalcaemia.

Persistent control – vitamin D deficiency

Vitamin D deficiency requires vitamin D2 (ergocalciferol) or D3 (cholecalciferol), with equal efficacy, preparations often combined with calcium and prescribed as two tablets, each containing 400 IU of vitamin D. These are relatively low doses and those with symptomatic vitamin D deficiency such as bone pain may need 50 000 IU weekly for a couple of months or 300 000 IU intramuscularly every 3 months. Hypercalcaemia secondary to vitamin D replacement is sometimes due to unrecognised, coexistent primary hyperparathyroidism.

Persistent control – hypoparathyroidism

In hypoparathyroidism or renal disease these doses of vitamin D are ineffective because PTH and healthy kidneys are needed for conversion to 1,25-dihydroxyvitamin D, and so calcitriol or alfacalcidol are needed, typically at starting doses 0.5 µg or 1 µg respectively. The main risk is nephrocalcinosis due to hypercalciuria.

1,25-hydroxyvitamin D deficiency in chronic kidney disease results in secondary hyperparathyroidism releasing calcium and phosphate from bone, correcting the hypocalcaemic tendency but at the expense of bone disease and phosphate accumulation, since the latter cannot be cleared in kidney disease. Treatment comprises oral phosphate binders and calcium as well as calcitriol. Newer agents such as a calcimimetic that reduce PTH secretion may become useful treatments as they do not increase the calcium phosphate product.

Whether PTH replacement or vitamin D replacement is optimal in hypoparathyroidism is not clear.

Is hypophosphataemia a problem?

This can be linked to decreased intake or absorption, vitamin D deficiency, liver disease or hyperparathyroidism. It causes organ dysfunction and along with potassium, magnesium and calcium disturbance should be corrected when low, as in, for example, re-feeding syndrome. It is available as oral phosphate or together with magnesium in magnesium glycerophosphate.

CASE 2.30 HYPONATRAEMIA

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr James Blonde, aged 58 years

Thank you for admitting Mr Blonde, who has had a week of diarrhoea and vomiting. He is now hypotensive (blood pressure 70/40), relatively bradycardic (heart rate 55) and tachypnoeic (respiratory rate 20). Examination is otherwise unremarkable. I obtained some blood tests yesterday and the results are appended. Blood tests taken a month ago were normal. His past medical history comprises hypertension, type 2 diabetes, Crohn's disease and a long-standing restrictive lung defect.

Yours sincerely

TEST RESULTS

Sodium 117 mmol/l, potassium 2.9 mmol/l, creatinine 800 mmol/l, urea 35 mmol/l, calcium 1.80 mmol/l, phosphate 3.11 mmol/l, magnesium 0.50 mmol/l, albumin 28 g/dl, INR 1.8, C-reactive protein 140, haemoglobin 13.2 g/dl, mean cell volume normal, white cell count 11.5 × 10^9/l, platelets 300 × 10^9 / l (venous blood gases show a marked acidosis – pH 7.05, $p\mathrm{CO}_2$ 4.7, $p\mathrm{O}_2$ 3.2, bicarbonate 7.3, base excess – 19.0, saturations 97%)

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr James Blonde is a 58-year-old man who has been unwell for a week with diarrhoea and vomiting. His stools are watery; there is no blood or mucus. He has had some cramping abdominal pains. He now feels exhausted and weak, and has been admitted to hospital because he has developed 'kidney failure'. He is a widower living alone in a bungalow and usually manages well. He mobilises in a wheelchair because of peripheral vascular disease and neuropathy from type 2 diabetes, but has a good degree of assistance with meals and washing from relatives and friends. He also has hypertension, a minor long-standing chronic lung condition which causes minimal breathlessness and Crohn's disease, the latter poorly controlled over the last few years. He carries his list of medications with him and concordance with treatment is excellent. His medications are – metformin, gliclazide, insulin, bendroflumethiazide, atenolol, ramipril, azathioprine and mesalazine. He is not really sure why his GP is so concerned; he feels that once he gets better and starts drinking again things will be all right.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

This is a complicated case, but the presentation of multiple acute problems on a background of multiple chronic diseases is now very common. The way forward is to take a standard history-taking approach to symptoms, with a full past medical history and drug history, and not to feel immediately swamped by the array of biochemical abnormalities. As you compile the information, consider potential triggers to each biochemical abnormality in turn.

Patient perspective

Explain that his GP was concerned that his current gastroenteritis illness has not just made him dehydrated but that his system may have become very sensitive to his medications while very dehydrated and unwell.

Past medical history

Take a list of each condition – type 2 diabetes, hypertension, Crohn's disease and a chronic respiratory condition – and explore the duration, complications and current symptoms of each; try to determine whether each is actively problematic or under control.

Drug and allergy history

The list of drugs is imperative because there are multiple iatrogenic contributors to his metabolic state.

Family history

Relevance here is unlikely.

Social history

Enquire fully into his home circumstances, his level of mobility and the degree of external support.

Discussion

How is fluid distributed throughout the body?

Water constitutes 60% of total body weight, equivalent to about 42 litres in a 70 kg man. Two-thirds of this is intracellular fluid (ICF) and one-third extracellular fluid (ECF).

SUMMARY BOX – ASSESSMENT AND PLAN

- Possible contributors to hyponatraemia include bendroflumethiazide, ramipril, diarrhoea and vomiting (with salt loss overriding the hypernatraemia seen in dehydration), hypoadrenalism, and pseudohyponatraemia (his blood glucose is unknown).
- Possible contributors to hypokalaemia include bendroflumethiazide and diarrhoea and vomiting. Hypomagnesaemia tends to have similar causes.
- Possible contributors to acute kidney injury include dehydration and ramipril on the background of diabetic nephropathy and renovascular disease. The raised C-reactive protein also suggests sepsis, and immunosuppression and diabetes lower the threshold for this.
- Possible contributors to hypocalcaemia include acute kidney injury (failure of conversion of inactive to active vitamin D) and malabsorption of vitamin D due to Crohn's disease.
- Possible contributors to the high international normalised ratio (INR) include malabsorption of vitamin K and sepsis.
- The acidosis is probably caused by acute kidney injury but diabetic ketoacidosis should be excluded.
- Immediate management includes fluid resuscitation and correction of life-threatening metabolic abnormalities. All drugs should be stopped and an insulin sliding-scale regimen started. Empiric antimicrobials might be considered.
- Calcium should be corrected first, before the acidosis, otherwise there is a risk of tetany.
- Hypokalaemia should also be corrected before acidosis, and can be given intravenously with magnesium.

The ECF is divided into interstitial fluid (ISF), which surrounds the cells (11–14 litres), and intravascular plasma (3–4 litres). They are separated by the capillary endothelium, which is permeable to low-molecular-weight solutes (e.g. sodium) but increasingly impermeable to high-molecular-weight solutes (e.g. albumin). The predominant ion composition of fluids is given in Table 2.68.

How are the ICF and ECF compartments maintained?

Compartmental distribution of water is primarily dependent on the 'osmotic pressure', which reflects the ion concentration gradients between compartments created by cellular ion pumps, such that sodium and chloride ions are mainly extracellular and potassium and phosphate ions intracellular. Thus, after a saline infusion the rise in extracellular sodium and chloride increases the osmotic pressure, drawing water out of the ICF and into the ECF compartment.

Table 2.68 Predominant ion composition of fluids

	Extracellular fluid	Intracellular fluid
Cations	Sodium (136–144 mmol / l)	Potassium (3.5–4 mmol / l) Magnesium
Anions	Bicarbonate Chloride (98–105 mmol / l)	Phosphate Proteins Organic acids

How is intravascular plasma volume and ISF balance maintained?

Fluid flow between plasma and interstitium depends on the balance between outward pressures (capillary hydrostatic pressure, tissue oncotic pressure) and inward pressures (ISF pressure, plasma oncotic pressure). Oncotic (colloid) pressure describes the ability of plasma proteins to bind and retain water in the circulation; albumin accounts for over 70%, haemoglobin about 20% and globulins less than 5%. Intravascular volume is thus determined by the 'oncotic pressure' of large-molecular-weight, non-diffusible vascular plasma proteins, circulatory hydrostatic pressure and the permeability ('leakiness') of vessels.

How does oedema arise?

Oedema results when ISF increases because of a pressure gradient or excess capillary permeability. The latter occurs in pathological conditions such as sepsis and surgery, and albumin leakage rises dramatically, reducing intravascular volume, whilst raised ISF albumin increases tissue oedema.

What are the normal intake and urine fluid volumes and sodium concentrations?

A healthy person might ingest 2.5 litres of water and 100 mmol of sodium daily (daily requirement 60–100 mmol) and lose 1.5–2.5 litres of water, 70–150 mmol of sodium and 40–70 mmol of potassium. A further 0.7 litres of 'insensible fluid loss' occurs as lung vapour and sweat; this can exceed 3 litres / day during illness, with high ambient temperature, fluid-losing enteropathies (e.g. diarrhoea), salt-losing renal failure or skin or mucous membrane losses (e.g. burns, ulcerative colitis). The daily urine output contains a total solute load of about 620–840 mosmol including sodium, potassium, urea and an array of other solutes. In healthy kidneys, maximum urine solute concentration is 1000 mosmol / l and to excrete the normal daily solute load a minimum urine output of 35 ml / h (0.5 ml / kg / h) is required.

What is osmolality?

Osmolality refers to the number of particles (osmoles) dissolved in 1 kg of solution (osmolarity refers to 1 litre rather than 1 kg). The main determinant of ECF osmolality is sodium and that of ICF osmolality is potassium. Normal plasma osmolality is 280–295 mosmol / kg. Normal urine osmolality is 50–1400 mosmol / kg (extremes, but commonly 500–800 mosmol / kg).

How is sodium regulated?

Sodium is the prime ECF cation, the prime determinant of ECF osmolality and thus the prime determinant of

ECF/ICF water distribution. The major sodium regulators are the kidney, aldosterone (Cases 2.14, 2.25 and 2.31) and antidiuretic hormone (ADH), otherwise known as vasopressin. ADH is the great evolutionary stress hormone – when sabre tooth tigers munched the limbs of our ancestors, ADH retained fluid by enhancing permeability at the collecting duct and made platelets sticky. Other contributors include atrial natriuretic peptide, angiotensin II (which may increase sodium reabsorption in the proximal tubule as well as promoting aldosterone), sympathetic nervous system activity (which also acts on the proximal tubule) and local paracrine factors such as endothelin-1, bradykinin and nitric oxide (which may inhibit sodium reabsorption in the collecting duct as well as altering vascular tone). Despite wide variations in salt and water intake the kidneys maintain extracellular sodium concentration and osmolality within a narrow range. The normal person described above drinking 2500 ml of water daily and producing 2000 ml of urine can maintain a serum osmolality of 285 and normal urine osmolality. A dehydrated person might ingest only a litre of water and produce a litre of urine (minimum daily output is 500–750 ml) but maintain the same serum and urine osmolalities. An excessive water drinker might ingest 5000 ml of water daily, produce 5000 ml of urine and maintain the same serum and urine osmolalities.

What happens to serum osmolality in dehydration?

Reduced body water leads to a rise in plasma osmolality, which is detected by osmotically sensitive neurons in the circumventricular organ of the hypothalamus which stimulate thirst and stimulate the paraventricular nucleus and supraoptic nucleus, the sites of ADH or 'sabre tooth tiger hormone'. During salt and/or water depletion ADH secretion increases urine concentration and reduces water clearance, while the renin–angiotensin–aldosterone system (RAAS) reduces urinary sodium (the response to sodium excess is less efficient and depends on passive suppression of the RAAS rather than on active elimination by natriuretic hormones, and so even in normal situations excreting a sodium load is a slow process). These mechanisms increase total body water and return plasma osmolality to the normal range. At around 284 mOsm/kg ADH thirst is switched off to prevent over-hydration.

What happens to salt and water in stress?

In acute illness the body retains salt and water. Total fluid retention may be more than 10 litres. It usually accumulates in the ISF, causing tissue or pulmonary oedema. Causative mechanisms include:

- ADH, RAAS and catecholamine-mediated antidiuresis and oliguria
- Impaired renal function with reduced free water excretion and urine-concentrating ability – when urine volume really must be, for example, 70 ml/h, to eliminate the increased solute load
- Catabolic urea production, which competes with sodium for excretion
- Potassium depletion due to RAAS activity, reducing sodium excretion
- Hyperchloraemia, which reduces glomerular filtration and causes sodium retention
- Na/K-ATPase pump failure due to reduced cellular energy causing intracellular sodium and water sequestration ('sick cell syndrome')
- Reduced intravascular volume due to increased albumin leakage (the systemic inflammatory response increases vascular permeability), which activates RAAS with further salt and water retention and worsening interstitial oedema.

What are the causes of hyponatraemia?

Hyponatraemia is the commonest electrolyte disturbance. Mild hyponatraemia (126–135 mmol/l) is very common. Hyponatraemia is usually caused by relative water gain or sodium loss but is far more often the result of excess water relative to sodium, in other words dilutional, with a low plasma osmolality indicating that water intake has exceeded water excretion. Hyponatraemia may be spurious or true.

Pseudohyponatraemia

Solutes that are impermeable to the cell membrane are osmotically active. Sodium and its accompanying electrolytes account for 86% of plasma osmolality. Therefore, hyponatraemia is usually synonymous with hypotonicity, but in two circumstances the hyponatraemia and osmolality are discordant:

- Hyperlipidaemia artificially lowers sodium while the directly measured osmolality is unchanged.
- Isotonic or hypertonic hyponatraemia may occur, e.g. hypertonic hyponatraemia due to hyperglycaemia; here it is preferable to measure plasma osmolality either using direct measurement or correcting the measured sodium for the glucose elevation (2.4 mmol / l decrease in sodium for each 5.6 mmol/l increase in glucose). Other solutes unaccounted for by the calculated osmolality (osmolality = $2[Na^+]$ + glucose = urea) can also elevate plasma osmolality when measured directly, giving rise to an osmolar gap (e.g. mannitol, methanol and ethylene glycol).

Thus, spurious (laboratory assay) hyponatraemia mostly occurs when lipid (hyperlipidaemias), glucose (diabetic ketoacidosis) or protein (paraproteinaemias) is high and plasma is hypertonic or isotonic. Parameters must be severely deranged to provoke significant pseudohyponatraemia – hereditary dyslipidaemia, severe ketoacidosis, or severe myeloma.

True hyponatraemia

True hyponatraemia is always dilutional, and hypotonic, with low plasma osmolality (hypo-osmolar) indicating that water intake exceeds renal capacity to excrete it. Since normal kidneys can excrete up to 30 litres of dilute urine (< 100 mOsm/kg) daily, hyponatraemia usually occurs when the kidneys fail to generate and excrete enough solute-free water to balance intake. True hyponatraemia occurs in four groups of settings (Table 2.69).

Note that teaching on assessment of hyponatraemia often promotes an algorithmic approach based on assessment of volume status as the starting point. There are three problems with this in the author's opinion: firstly, volume status is not always reliably assessed by junior and senior doctors alike and this mistake at the start of the 'algorithm' will lead to improper further assessment; secondly, volume status is not always 'true' to the cause (for example, thiazides and hypoadrenalism cause renal sodium loss and may cause hypovolaemia, but this is not always so); thirdly, the cause is often multifactorial. For these reasons it is the author's experience that many doctors find the whole business of hyponatraemia assessment a jungle in which they are easily lost, and resort resignedly to checking urine and serum osmolalities without really appreciating why.

For all of these reasons the author thinks it preferable to consider the logical checklist of causes in Table 2.69 and then consider if each in turn might be relevant to a particular patient, taking appropriate action for each potential cause; volume status is included in the table for those who like to see where it should fit.

What are the consequences of hyponatraemia?

When exposed to a hypotonic environment, cells tend to swell. The symptoms and signs of hyponatraemia depend on both its severity and the rapidity of the fall. Cerebral oedema is more likely the faster the fall. The body hates cell swelling, particularly the brain in its closed cavity where it can cause seizures and ultimately death. ADH levels are therefore normally low. Relative ADH excess plays a role in most causes of hyponatraemia because the body sees sodium as the instigator of cell swelling and water as the innocently seduced bystander. Hypernatraemia is therefore rare.

Clinical features and rate of change

Although an arbitrary division, hyponatraemia is considered acute if it develops within 48 hours and chronic if longer. The former provokes brain oedema, causing nausea and malaise when serum sodium is 125–130 mmol/l. Headache, altered cognition, seizures, coma and death may ensue when below 110–115 mmol/l. Although chronic hyponatraemia is considered asymptomatic above this level, subtle symptoms may be present such as lethargy and altered cognition and a propensity to falls.

Brain adaptation

Brain cells start to adapt to hyponatraemia after 48 hours by limiting production of intracellular solutes and by shifting solutes to the extracellular compartment (ECC), to balance extracellular hypo-osmolality and maintain cell volume, thereby protecting themselves from cell oedema. These adaptive mechanisms take time to develop fully.

What is central pontine myelinosis?

Correcting hyponatraemia rapidly (> 10–12 mmol/l/day), especially in chronic and adaptive states, causes fluid to shift from the intracellular compartment (ICC) to the ECC. Consequently, the brain tries to limit cell shrinkage by the reuptake of solutes to prevent water escape. But this reuptake is slower than the initial loss and the brain cells shrink as a result of a net fluid loss, resulting in osmotic demyelination in different parts of the brain, notably the pons (e.g. spastic quadriparesis and pseudobulbar palsy). Extrapontine myelinosis occurs in a small proportion of cases (e.g. ataxia). Symptoms typically start 2–3 days after correction. Particular risk factors for osmotic demyelination are alcoholic cirrhosis and hypoxia, while premenopausal women and endurance athletes are at high risk of brain damage or death from hyponatraemia.

How should hyponatraemia be treated?

Treatment principles

Establishing and treating the cause is essential. Hyponatraemia itself can be corrected by fluid restriction, salt replacement, a vasopressin (ADH) antagonist or a combination of the three.

- In hypovolaemia, correcting fluid depletion with 0.9% normal isotonic saline will correct the relative water excess. If chronic, caution is needed as euvolaemia will suppress vasopressin (ADH), causing water diuresis and accelerated correction of sodium. Therefore, vasopressin use may be required to slow down sodium rise.
- In hypervolaemia treatment of the underlying disorder and fluid restriction alone or with a vasopressin antagonist are indicated.
- In euvolaemia (usually syndrome of inappropriate ADH excess) water restriction with or without salt replacement is indicated. Hypertonic saline could be used in severe symptomatic cases with the caveats below, but isotonic saline will result in further lowering of sodium owing to increased net sodium excretion because water, not sodium handling, is at fault in the kidneys. Newer vasopressin antagonist drugs can be used in hypervolaemic and euvolaemic hyponatraemia, causing aquaresis through blocking the vasopressin effect on V2 receptors in the collecting duct.

Correction rates

The general principle is that the rate of correction should be closely linked to the rate of development. However, in the practical setting, it may difficult to distinguish between acute and chronic onset and a more appropriate approach is to correct slowly regardless of cause and time frame wherever possible, and on the basis of symptoms.

Table 2.69 The four settings of true hyponatraemia

	Causes	Volume status	Clinical signs	Biochemical changes	Treatment
Psychogenic polydipsia	Excess water drinking	Euvolaemic	Excess drinking High urine output	Hyponatraemia Urine sodium < 20 mmol / l Urine osmolality ↓	Water restriction
Unavoidable sodium loss	**Renal losses** Diuretics (thiazides commonest cause) Tubular dysfunction (e.g. renal tubular acidosis, salt-losing nephropathy, metabolic alkalosis) Hypoadrenalism (especially if postural hypotension) Cerebral salt wasting (hyponatraemia in brain injury is often assumed to result from SIADH but it may also result from natriuretic peptide release causing natriuresis and diuresis) **Extrarenal losses** Gastrointestinal loss Pancreatitis Skin loss in burns / severe dermatitis	Hypovolaemic / dehydrated	Tachycardia Hypotension Low JVP Decreased skin turgor Dry mucous membranes	Raised urea **Renal losses** Natriuresis (urine sodium > 20 mmol / l) suggests renal losses (thiazides the commonest cause), or less commonly hypoadrenalism – arrange a synacthen test if postural hypotension Urine osmolality ↑ / → **Extrarenal losses** The physiological response in non-renal losses via the renin–angiotensin–aldosternone system is sodium conservation leading to associated low urinary sodium (< 20mmol / l) Urine osmolality ↑	Rehydration Treat cause (in practice urine sodium measurement is seldom undertaken and it may be appropriate merely to stop a potentially offending thiazide, for example, and assess response)
Appropriate ADH excess (body perceives volume depletion)	Cardiac failure Cirrhosis Nephrotic syndrome	Hypervolaemic / oedematous	Peripheral, sacral and pulmonary oedema Ascites Raised JVP (excess sodium and water but water gain proportionately greater)	Urine sodium < 20 mmol/ l Urine osmolality ↑	Treat cause Water restriction
SIADH	Tumours, e.g. lung, mesothelioma, ureteric, pancreatic, duodenal, lymphoma, endometrial, leukaemia Lung disease, e.g. abscess, empyema, pneumonia Central nervous system disease, e.g. tumour, abscess, hydrocephalus, haemorrhage, meningitis, encephalitis, acute intermittent porphyria, dementia Drugs, e.g. phenothiazines, tricyclics, ecstasy, carbamazepine, cyclophosphamide, selective serotonin reuptake inhibitors	Euvolaemic	Signs of underlying cause	Urine is inappropriately concentrated in the face of hyponatraemia. Essential diagnostic criteria are: Plasma osmolality < 270 mOsm / kg Inappropriate urinary concentration (UOsm > 100 mOsm/ kg) Elevated urinary sodium (> 20 mmol / l) in presence of normal salt and water intake Normal extracellular volume Exclusion of hypothyroidism and glucocorticoid deficiency	Water restriction to 800–1200 ml / day Demeclocycline (inhibits ADH at the distal tubule, inducing nephrogenic diabetes insipidus) and may take a few days to work

ADH, antidiuretic hormone; JVP, jugular venous pulse; SIADH, syndrome of inappropriate ADH excess.

- For acute hyponatraemia with severe symptoms (e.g. seizures), 1.8–3% hypertonic saline is advocated by some with the aim of elevating sodium levels by 1.0 mmol/h in the first 2–3 hours or until symptoms disappear, while keeping the target for the first 24 hours below 10 mmol/l to avoid osmotic demyelination. This can be achieved only with close monitoring, invariably in an intensive care setting, and there are many who would not advocate hypertonic saline under any circumstances because of the risks. Doubtless the biggest risk, however, is failure to appropriately monitor in a busy hospital ward with inadequate understanding of the problem and its risks and inadequate handover between changing staff.
- For chronic hyponatraemia with no or mild symptoms, slower methods of correction (e.g. fluid restriction to 500 ml/day below the daily urine volume) may be appropriate. For symptomatic chronic hyponatraemia, there is a high risk of neurological complications with correction and a lower correction rate than for acute hyponatraemia is used to increase sodium by 0.5 mmol/h in the first few hours, with total correction no more than 10 mmol/l/day to avoid osmotic demyelination. Treatment should be halted if there is cessation of symptoms or sodium reaches 120 mmol/l or a 10 mmol/l increase occurs within the first 24 hours. There needs to be a very good reason for actively infusing hypertonic saline rather than fluid restriction alone.

What are the causes of hypernatraemia?

Hypernatraemia always denotes hypertonic hyperosmolality with ICC shrinkage. Even if there is salt-free water diuresis (e.g. diabetes insipidus) hypernatraemia does not ensue unless there is low free water intake, such as in limited availability (humans in deserts are physiologically different from camels) or in a blunted thirst mechanism (hypothalamic lesion). Causes of hypernatraemia are shown in Table 2.70, but dehydration is by far the commonest cause.

Table 2.70 Causes of hypernatraemia

Net water loss	Hypodipsia Diabetes insipidus
Hypotonic fluid loss	**Renal loss** Loop diuretics Osmotic diuresis (hyperglycaemia, mannitol infusion) Polyuric phase of acute tubular necrosis **Extrarenal loss** Vomiting, diarrhoea Nasogastric drainage Osmotic laxative Cutaneous loss (burns, excessive sweating)
Hypertonic sodium gain	Hypertonic sodium bicarbonate infusion Hypertonic feeding preparation Ingestion of sodium chloride Hypertonic sodium chloride infusion Primary hyperaldosteronism

What are the consequences of hypernatraemia?

Some cell shrinkage occurs in hypernatraemia, but the brain reacts by solute uptake to shift water from the ECC to the ICC, thereby preventing cell shrinkage. But severe (> 160 mmol/l) or rapid onset (< 12 hours) hypernatraemia can lead to intracranial bleeding, convulsion and coma.

How is hypernatraemia treated?

Treatment is of the underlying cause and by lowering serum sodium with hypotonic fluid. It is safest to administer fluid orally or enterally. If intravenously, it should be hypotonic (0.45% hypotonic saline or 5% dextrose) unless isotonic fluid is required because of haemodynamic compromise. The same general principles are followed for rates of correction as for hyponatraemia (1 mmol/l/h with the aim of not exceeding 10–12 mmol/l/24 hours for acute hypernatraemia and no more than 0.5 mmol/l/h in chronic hypernatraemia to avoid brain oedema and prevent potential osmotic demyelination).

To estimate the change in sodium following the infusion of 1 litre of fluid, the following formula may be used: change in Na^+ = infusate Na^+ (mmol/l) − serum Na^+ (mmol/l)/total body water (0.5 and 0.613 of body weight in kg in women and men, respectively). The sodium correction required per unit time is then divided by the change in sodium from the formula to obtain the fluid volume to effect that correction. Measured and insensible fluid loss allowance is added to make up the final volume to be infused over that time. As ever, close monitoring is the best option.

What are the causes of polyuria?

Polyuria occurs because of primary polydipsia, which is rare (e.g. compulsive water drinking, hypothalamic infiltration), or diabetes insipidus (Box 2.84). Primary polydipsia is sometimes referred to as dispogenic diabetes insipidus.

What is the water deprivation test?

This is a two-step test.

Box 2.84 Diabetes insipidus

This is the result of antidiuretic hormone (ADH) deficiency or resistance to its action.

Cranial or hypothalamic diabetes insipidus

This is uncommon, because 80% of ADH-secreting neurons must be destroyed. It may be primary (possibly autoimmune) or secondary to trauma, tumours, craniopharyngioma, radiotherapy, infiltration (granulomatous, haemochromatosis), infection, human immunodeficiency virus, pregnancy (placental vasopressinase) or vascular compromise (Sheehan's syndrome, post-coronary artery bypass grafting).

Nephrogenic

This may be primary, or secondary to chronic kidney disease, metabolic disturbance (hypokalaemia, hypercalcaemia), drugs (lithium is the commonest cause, accounting for 15% of nephrogenic diabetes insipidus, demeclocycline), osmotic diuresis (glycosuria, poorly controlled diabetes) or systemic disease with tubular damage (amyloid, sickle cell disease, myeloma).

1. Dehydration step: 8-hour water deprivation

Normally a rise in osmolality stimulates osmoreceptors to promote ADH release and urine output falls, with a healthy rise in urine osmolality to > 700 mOsm/kg. Theoretically, primary thirst disorders have normal physiology and should respond to dehydration with appropriate urine concentration, whereas diabetes insipidus (cranial or nephrogenic) is unable to respond and urine remains dilute.

2. Desmopressin step

If diabetes insipidus is suspected, desmopressin is administered subcutaneously or intramuscularly. Cranial diabetes insipidus responds with a rise in urine osmolality, while nephrogenic diabetes insipidus does not. Desmopressin is thus a suitable treatment for cranial diabetes insipidus.

What are the principles of fluid management on a medical ward?

Daily fluid administration is essential on most medical wards. However, under- and over-hydration are common and associated with significant morbidity and mortality. Three key issues contribute to poor fluid management:

1. Failure to understand the principles of fluid balance, with inappropriate fluid prescription in relation to available fluid balance information (serum electrolyte data, input/output charts, daily weights)
2. Poor documentation of fluid balance
3. Fluid prescription often being delegated to less experienced members of the team.

Fluid is best delivered by the oral or nasogastric route, but intravenous fluid may be required in patients unable to drink (or absorb), with excessive fluid losses or requiring resuscitation. The aims are to replace normal fluid and electrolytes, provide additional resuscitation fluids, maintain circulation appropriate to tissue metabolism and waste removal, and ensure a stable intra- and extracellular milieu to preserve membrane potential and transport mechanisms.

Assessing fluid balance

In most patients, clinical assessment is adequate, with review of fluid input and output, non-invasive monitoring of vital signs, and measurements of serum (and occasionally urinary) electrolytes and urea. In some unstable patients the cardiovascular responses to serial 'fluid challenges' is used to determine the need for volume replacement but this response is not always reliable as it is influenced by venous tone and does not have a linear relationship with cardiac output. Other measures of inadequate tissue perfusion include an increase in serum lactate and mixed venous saturation below 70%. Complex cases may need non-invasive transoesophageal Doppler or invasive cardiac monitoring to assess cardiac output and filling pressures.

Fluid choice and administration

With the exception of 5% dextrose, almost all intravenous solutions contain sodium and chloride, some in near physiological concentrations (e.g. Hartmann's) and others in supra-normal amounts (e.g. 'normal' (0.9%) saline with 154 mmol/l of both sodium and chloride). The excess chloride increases the risk of hyperchloraemic acidosis.

- *Crystalloids* contain low-molecular-weight salts (e.g. sodium chloride) and sugars (e.g. glucose) which dissolve completely in water and pass freely between intravascular and interstitial compartments. Although usually isotonic, they redistribute rapidly (1–4 hours) following infusion from the intravascular to other fluid compartments. Thus large volumes are required to maintain intravascular volume and interstitial oedema often occurs. Low-sodium fluids (e.g. 5% dextrose) disperse throughout all fluid compartments, whereas sodium-containing fluids (e.g. 0.9% saline) have a smaller volume of distribution because cellular pumps remove sodium from ICF limiting the fluid to the ECF.
- *Colloids* contain complex, high-molecular-weight molecules exerting an oncotic pressure and are retained in the vascular compartment for longer. But studies show no advantage over crystalloids for initial resuscitation. Both natural (e.g. albumin) and synthetic (e.g. gelatin, hydroxyethyl starch, dextran) colloids are expensive with specific properties and side effects, including allergic reactions and clotting abnormalities.
- *Sodium bicarbonate* (1.26%) is used in patients with metabolic acidosis (pH ≤ 7.2) due to renal failure or gastrointestinal losses, advocated in acute kidney injury guidelines.
- *Blood* is most appropriate for haemorrhagic loss to maintain haemoglobin concentration above 8 g/dl, but young people and those with renal disease, haemoglobinopathies or chronic anaemia

Table 2.71 Fluid choices

Scenario	Fluid choice
Maintenance fluid in stable euvolaemic patients with normal renal function	1–1.5 ml / kg / h water, 70–150 mmol sodium and 40–70 mmol potassium daily – in an 80 kg person, this equates to 1 litre of normal saline and 2 litres of 5% dextrose with 20–40 mmol potassium in each litre of 5% dextrose; some recommend physiologically balanced solutions (PBS, e.g. Hartmann's) as maintenance when larger volumes are required as these reduce chloride load (5% dextrose and 4%/0.18% dextrose / saline are important sources of free water for maintenance, but should be used with caution beyond maintenance since they may cause hyponatraemia; the exception is significant free water deficit states, e.g. diabetes insipidus)
Significant hypernatraemia	5% dextrose
Significant hyponatraemia	0.9% saline
Sepsis	Immediate (if hypotensive or if lactate raised) 20–40 ml / kg PBS in aliquots of 0.5–1 litres based on clinical response If hypotension or lactate elevation persist, central monitoring and continued resuscitation with Gelofusine 1–1.5 litres then 1–1.5 litres
Acute kidney injury	Reduces ability to excrete fluid and electrolytes so significant risk of fluid and sodium overload and hyperkalaemia Large volumes of crystalloid or colloid engender large solute loads that are difficult to excrete and precipitate hyperchloraemic acidosis PBS containing potassium causes less acidosis; if hyperkalaemia develops non-potassium-containing crystalloid solutions (e.g. 4%/0.18% dextrose/saline or 0.45% saline) are used 0.9% saline is only used in hypochloraemia (e.g. vomiting)
Established oliguric or anuric renal failure	Fluid replacement restricted to insensible loss (0.5–1 litre daily)
Significant bleeding	Blood (takes time to prepare) Start with 20–30 ml/ kg PBS, followed by 1–1.5 litres Gelofusine (1–1.5 litres) + / – HES
Head injury (hyponatraemia, hypoxia, hypotension and hyperthermia worsen brain oedema)	0.9% saline

Hydroxyethyl starch; PBS, physiologically balanced solution.

may tolerate lower levels. A haemoglobin of about 10 g/dl improves outcome in cardiac patients.

Fluid selection is guided by the underlying condition, ECF status, fluid losses, renal function and electrolyte concentrations. Common scenarios are in Table 2.71.

During resuscitation it is not unusual for patients to be given many litres of normal saline. Since normal excretion of waste solutes (e.g. urea) and electrolytes is about 700 mosmol/day, and assuming a degree of renal impairment with loss of concentrating ability, it may only be possible to excrete a small function of the 'additional' normal saline solute load each day. The retained chloride may cause hyperchloraemic acidosis.

CASE 2.31 POISONING AND METABOLIC DISTURBANCE

Candidate information

Role

You are a doctor in the emergency medical admissions unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Ms Anita Radcliff, aged 24 years
Thank you for admitting this young lady who has taken an overdose of paracetamol following an argument with her boyfriend. She took the overdose yesterday evening and came to the surgery today to tell somebody.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Ms Anita Radcliff is a 24-year-old woman who took thirty 500 mg paracetamol tablets last night, around 12 hours ago. She also took 28 aspirin tablets, alcohol and some undetermined 'recreational' substances purchased over the internet. She subsequently feels a little anxious and breathless. She has no medical history of note, with no history of psychiatric disease or suicide attempts. She has now been admitted to hospital, having seen her GP. She did not want to die but took the overdose on impulse following an argument with her boyfriend. She subsequently told a friend what had happened who told her that paracetamol could cause liver damage and persuaded her to see her doctor. She is unaware that aspirin is also dangerous and will not volunteer this information to a doctor unless asked about other tablets. She also thinks she might be pregnant as she has missed her period and has not got around to telling her boyfriend this. She is now keen to go home if a blood test is normal.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Establish facts about the overdose.** Establish exactly what was taken, and when. Through a careful, empathetic approach, assuring her of confidentiality and that you are here to help, she will be likely to tell you exactly what she took, but ask specifically about other tablets as well as paracetamol. Explain that the first, urgent, thing to do is to take blood for paracetamol and salicylate levels. The fact that she is breathless could represent anxiety, but acid–base disturbance from salicylate poisoning must go through your mind.

■ **Establish events around the overdose.** Ask about events preceding the act, reasons for the act, suicide intent and support networks.

■ **Assess suicide risk.** Ask if she took the overdose alone, about precautions to avoid discovery, whether with active preparation or on impulse, and why she alerted her friend and agreed to see her GP. Ask how she feels now about life.

Patient perspective

Show empathy. She is probably frightened. Assure her that you will firstly ascertain whether her overdose needs treatment, and that you can also establish whether or not she is pregnant, as this could have a bearing on monitoring and treatment.

Past medical history

Establish that there is no past history of psychiatric disease.

Drug and allergy history

Ask about all drugs including non-prescription ones.

Family history

Establish if there is any family history of psychiatric disease.

Social history

Ask about alcohol and drugs.

SUMMARY BOX – ASSESSMENT AND PLAN

- Urgent blood tests include routine haematobiochemistry with liver function (the international normalised ratio is especially important), paracetamol and salicylate levels, arterial blood gases and a pregnancy test (urine or blood β-human chorionic gonadotrophin).
- She should be treated with *N*-acetylcysteine (Parvolex) according to the nomogram.
- If she is pregnant then her case should be discussed with your consultant and potentially the poisons information service and an obstetrician.
- She should stay in hospital until it can be established that she is well and her blood tests are satisfactory, and until she has seen a psychiatrist.

Discussion

How is acid–base balance regulated?

Acids are hydrogen ion (H^+) donors and bases are H^+ acceptors. The main source of H^+ is oxidation of carbon compounds ($CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$). Buffers minimise changes in pH either by binding H^+ or by dissociating to release H^+. Buffers include intracellular fluid (50%) and plasma bicarbonate, phosphate, proteins and red cells.

What acid–base balance disturbances do you know of?

These are listed in Table 2.72.

pH reflects H^+ concentration on a logarithmic scale such that a small change in H^+ concentration causes a large change in pH. It may not therefore take very long in acute illness with lactic acid accumulation to fall from a normal pH of 7.4 to, for example, 7.1. However, CO_2 has a direct

Table 2.72 Types of acid–base disturbance

Principal disturbance	Primary change	Secondary compensation
Metabolic acidosis	↓ HCO_3	↓ pCO_2
Metabolic alkalosis	↑ HCO_3	↑ pCO_2
Respiratory acidosis	↑ pCO_2	↑ HCO_3
Respiratory alkalosis	↓ pCO_2	↓ HCO_3

relationship with ventilation; if breathing at 5 l/min were to give a pCO_2 of 5 kPa, then breathing at 2.5 l/min would give an increased pCO_2 of 10 kPa, and if hyperventilating at 10 l/min the pCO_2 would fall to 2.5 kPa. Metabolic disturbances might be analysed by the bicarbonate or the base excess or deficit, the latter simply implying the amount of base needed to return the pH to normal.

Note that the pH gives the primary disturbance (acidaemia or alkalaemia), and this is useful to remember when interpreting arterial blood gases where there is compensation. For example, a patient with a high pH, hypocapnia, a low bicarbonate and appreciably negative base excess has primary respiratory alkalosis with metabolic compensation – the pH may correct with metabolic compensation but will not overshoot and overcorrect, i.e. this example could not be primary metabolic acidosis with respiratory compensation, although there is one exception in this example and that is salicylate poisoning because salicylates both stimulate the respiratory centre and cause metabolic acidosis to provoke a mixed picture. A patient with chronic obstructive pulmonary disease and primary respiratory acidosis may have a raised bicarbonate but this metabolic compensation will not overcorrect the pH to produce alkalosis. A patient with primary metabolic acidosis may hyperventilate with respiratory compensation but the hyperventilation will not tend to overcorrect the pH and produce alkalosis.

What are the causes of metabolic acidosis?

These can be associated with an increased or a normal anion gap.

$$\text{Anion gap} = \text{plasma (sodium} + \text{potassium)} - (\text{chloride} + \text{bicarbonate})$$

$$\text{i.e. normal anion gap} = (146 + 4) - (110 + 24)$$

The normal value is 16 ± 2 mmol/l. The 'gap' comprises unmeasured anions such as albumin, phosphate and sulphate.

Increased anion gap metabolic acidosis

This is usually the result of the addition of endogenous or exogenous organic acid. A mnemonic for remembering its causes is KUSMALE – think of Kussmaul breathing in diabetic ketoacidosis (Table 2.73).

Table 2.73 Causes of increased anion gap metabolic acidosis

	Anions	Features
Ketoacidosis	Ketotic pathway	Diabetic ketoacidosis
Uraemia	Organic acids	Renal failure
Salicylate poisoning	Salicylic acid	Also respiratory alkalosis
Methanol poisoning	Formic acid	Visual disturbance
Alcohol / starvation	Ketotic pathway	
Lactic acidosis	Lactic acid	Ischaemia / infarction / sepsis
Ethylene glycol	Glycolate / oxalate	Oxalate crystals / renal failure

Normal anion gap metabolic acidosis

This is usually the result of loss of bicarbonate. Compensatory chloride retention maintains a normal gap and hence this is sometimes described as hyperchloraemic (and often hypokalaemic) metabolic acidosis. Causes include:

- Diarrhoea (loss of bicarbonate)
- Ureterosigmoidostomy (loss of bicarbonate)
- Renal tubular acidosis (RTA) (loss of bicarbonate in proximal RTA, impaired H^+ excretion in distal RTA)
- Ammonium chloride
- Acetazolamide.

What are the causes of metabolic alkalosis?

Metabolic alkalosis is caused by a loss of H^+ or the addition of bicarbonate. Gastrointestinal H^+ losses include vomiting and intestinal secretions. Renal losses include diuretics, hyperaldosteronism, Cushing's syndrome and liquorice ingestion.

What are the causes of respiratory acidosis?

Respiratory acidosis is caused by hypoventilation.

What are the causes of respiratory alkalosis?

Respiratory alkalosis is caused by hyperventilation, e.g. anxiety, salicylate overdose, hypoxia (e.g. pulmonary embolism), fever, thyrotoxicosis.

Do you know anything about ethylene glycol and methanol poisoning?

Ethylene glycol is a constituent of antifreeze and screen wash. Toxicity is characterised by a severe high anion gap metabolic acidosis and calcium oxalate crystals in the urine. Following ingestion, peak serum concentration is reached in 1–4 hours and the sequence of clinical events is as follows:

- Stage 1 (30 min–12 hours): central nervous system disturbances
- Stage 2 (12–24 hours): metabolic acidosis and cardiopulmonary effects
- Stage 3 (24–72 hours): acute renal failure.

Symptoms of methanol toxicity include weakness, nausea and headache. Eye effects include reduced vision, mydriasis and hyperaemia of the optic disc. Optic atrophy secondary to optic nerve anoxia can lead to blindness.

Treatments for ethylene glycol or methanol intoxication include fomepizole (first-line), ethanol and haemodialysis.

What is the role of the proximal tubule and what disorders can occur here?

Exchange of H^+–Na^+ occurs in the proximal tubule, providing luminal H^+ for reclaiming most filtered bicarbonate. Two-thirds of filtered Na^+ (the prime determinant of extracellular fluid volume) and 80% of filtered water are reabsorbed here. Glucose and amino acids are reabsorbed completely here via a carrier protein. Also reabsorbed are phosphate (80%), urate (90%), potassium, chloride, calcium, urea (each approximately 50%) and a small amount of magnesium.

Glycosuria occurs when the 'renal threshold' for reabsorption (plasma glucose 10 mmol/l) is exceeded, as in diabetes mellitus or in a genetic defect in the sodium–glucose transporter. Various aminoacidurias (e.g. Hartnup's disease, homocystinuria, cystinuria) result from defective amino acid transporters. In cystinuria there is excess secretion of cystine, ornithine, arginine and lysine (COAL), causing high urinary cystine levels and calculi. This is not the same disease as cystinosis, in which intracellular accumulation of the amino acid cystine disrupts tubular transport and can lead to renal Fanconi syndrome (failure of proximal tubule function) and renal failure. RTA can also affect the proximal tubule.

What is the role of the loop of Henle, and how do loop diuretics work?

The loop of Henle comprises a proximal straight tubule, a thin descending limb, and thin and thick ascending limbs. It reabsorbs important additional sodium, water, potassium, chloride, calcium and magnesium. A Na^+/K^+–ATPase pump in the basolateral (non-luminal) membrane exchanges these two ions to maintain a baseline low intracellular sodium concentration, but this encourages sodium influx via the apical (luminal) membrane from the lumen, and this is coupled with one potassium and two chloride ions in a unique 'triple co-transporter' (sodium, potassium, chloride) carrier molecule.

Loop diuretics bind to the chloride site of this carrier molecule and inhibit triple co-transport and water transport. A potassium channel normally redirects some intracellular potassium back into the lumen, but loop diuretics inhibit this too and encourage a gradient for calcium and magnesium to efflux into the lumen. Traditional thinking was that diuretics prompted compensatory aldosterone action on an H^+–Na^+ pump and that the resultant loss of H^+ caused alkalosis. However, loop diuretics seem to also enhance local bicarbonate uptake as the H^+–Na^+ pump operates faster to compensate for the diuretic action. Therefore, loop diuretics cause a hyponatraemic, hypokalaemic, hypomagnesaemic, hypocalcaemic, hypercalciuric (predisposing to calculi) metabolic alkalosis.

What is Bartter's syndrome?

Bartter's syndrome is a genetic defect of the triple co-transporter and numerous mutations have been described. It is a genetic loop diuretic.

How do thiazide diuretics work?

Fluid entering the distal tubule is hypo-osmotic. Here an apical sodium chloride co-transporter promotes sodium (and chloride) reabsorption (such that final excretion is < 1% of what is filtered) and calcium efflux into the lumen. Thiazide diuretics block the co-transporter and cause similar biochemical changes to loop diuretics, except that they may cause hypercalcaemia.

What is Gitelman's syndrome?

Gitelman's syndrome is a genetic defect of the above co-transporter. It is a 'genetic' thiazide.

What is the role of the terminal distal tubule and what is the effect of aldosterone here?

Aldosterone is secreted by the zona glomerulosa of the adrenal cortex in response to raised angiotensin II and high plasma potassium. It stimulates the absorption of Na^+ ions (via an H^+–Na^+ pump and apical Na^+ channel), exchanging these for K^+ and H^+. Some potassium-sparing diuretics inhibit aldosterone. Aldosterone disorders are discussed in Case 2.14 (Hypertension) and the role of aldosterone in potassium disorders is discussed in Case 2.25 (Acute kidney injury).

What is the role of the collecting duct and antidiuretic hormone (ADH)?

The final common regulator of volume is ADH, which binds to the vasopressin-2 receptor (AVPR-2) on the basolateral membrane of the collecting duct. An intracellular cascade promotes insertion of the water-permeable channel aquaporin-2 into the apical membrane. A defective AVPR-2 or aquaporin-2 causing end-organ resistance to ADH gives rise to nephrogenic diabetes insipidus (Case 2.30).

What is RTA?

Various abnormalities of tubule mechanisms give rise to the normal anion gap hyperchloraemic metabolic acidosis of the various types of RTA. Type 1 RTA and type 2 RTA cause hypokalaemia; type 4 RTA causes hyperkalaemia. Renal function is often normal, although RTA is commonly a feature of acute kidney injury with tubulointerstitial nephritis.

Type 1 or distal RTA

The cells of the distal nephron normally acidify urine. Because of a defective apical H^+–ATPase in the distal tubule, the tubule cannot excrete H^+ or reabsorb sodium. This stimulates aldosterone, causing hypokalaemia. Bicarbonate buffering decreases serum bicarbonate levels (and reclamation of bicarbonate is functionally linked to H^+ secretion by H^+-ATPase) and bone buffering leads to release of calcium. Causes include autoimmune diseases such as systemic lupus erythematosus, hypergammaglobulinaemia, nephrocalcinosis (primary hyperparathyroidism, vitamin D excess, medullary sponge kidney), tubulo-interstitial damage from drugs such as non-steroidal anti-inflammatory drugs and tubule pressure damage in obstructive uropathy. Patients may present with hypokalaemic complications, renal calculi or bone pain (late). Diagnosis is by serum biochemistry and is confirmed by alkaline urine, which fails to acidify to pH > 5.2 following an ammonium chloride acid load.

An autosomal recessive form of distal RTA is caused by a mutation in the apical H^+-ATPase. Some patients develop sensorineural hearing loss, probably because of a defective cochlear H^+-ATPase. An autosomal dominant form of distal RTA is recognised because of mutations in *AE1*, a basolateral chloride–bicarbonate anion exchanger which must be fully operational if bicarbonate reclaimed from lumen to tubule cell is to progress onwards from tubule cell to bloodstream.

Type 2 or proximal RTA

The H^+-Na^+ pump in the proximal tubule operates but only slowly, so that bicarbonate recovery is slow. Causes include paraproteinaemias (amyloid), cystinosis, drugs and Wilson's disease, which may also induce wider proximal tubule damage resulting in renal Fanconi syndrome (failure to reabsorb glucose, phosphate and organic amino acids). Diagnosis is by serum biochemistry and detection of alkaline urine (bicarbonaturia). The urine can acidify because there is slowing rather than complete inhibition of normal function.

Type 4 RTA (associated aldosterone deficiency or resistance)

Aldosterone deficiency may be primary (Addison's disease) or secondary (to hyporeninaemia). Aldosterone resistance may be congenital (pseudohypoaldosteronism) or acquired (angiotensin-converting enzyme inhibitors, potassium-sparing diurectics, systemic lupus erythematosus, amyloid, obstructive uropathy, diabetes). See also Case 2.14, Box 2.41, for disorders of aldosterone; Case 2.25, Table 2.56, for disorders of potassium related to aldosterone.

What is the current profile of drug addiction?

Addiction to substances, including alcohol, cigarettes (nicotine/tobacco and in ascending order of faster brain entry, worse effects and addiction chewing tobacco, snuff, cigarettes) and an alarming array of 'recreational' drugs', is now of the order, medically and economically, of cardiovascular disease, cancer and mental illnesses. It occupies a large slice of the acute medical intake in most hospitals and should probably be considered a mental illness given the complex interplay of social, individual biological, and drug factors which determine the type of presentation. Harm may occur from:

- Acute toxicity
- Withdrawal (after withdrawal, brain changes promote perpetuation of behavioural changes and addiction)
- Chronic effects
- Addiction
- Route of use – infections, skin disease, lung disease.

As well as transmissible viruses a vast array of infections afflict intravenous drug users including cellulitis, deep tissue infections, necrotising fasciitis, psoas abscesses (inability to straighten the leg a clue), infective endocarditis and deep vein thrombosis with secondary infection. The practice of needle licking (a culture medium) introduces oral bacteria, and other problems include dissolving of substances in lemon juice (a culture medium), skin popping and poor dental hygiene.

Traditional drugs of misuse

In terms of relative harm, heroin is hugely harmful, followed by cocaine, amphetamines, 'ecstasy' and cannabis. Drug abuse is a problem that affects all classes. Cocaine and ecstasy are commonly used by young working people, and amphetamines are stimulants used by long-distance drivers and military personnel.

Novel recreational drugs

Novel recreational drugs taken for euphoria, stimulation, sexual arousal or other reasons may be extremely harmful but 'legal', and the internet is a common source of these. Purchasers do not know what they are buying, and what is perceived to be the same drug as previously purchased can be entirely different. For example, benzylpiperazine (BZP), a catathione and caffeine may all be packaged to look the same, and caffeine itself may be in huge doses that provoke hypokalaemia, arrhythmias and death; 90% of such drugs are made in South East Asia, mostly in China, in vast illegal factories employing highly qualified scientists. The drugs are then shipped as white powder, and, since millions of white powders are imported into the UK daily, identifying illegally imported drugs is increasingly challenging. Drugs may then be sold via street-level dealers or from high street 'head-shops' (and other outlets including newsagents), as well as via the internet where they are marketed attractively, often as bath salts or plant food and with attempts by vendors to retain legality by adding 'not for human consumption'. A key problem is that such drugs evolve rapidly, simply by modification of compounds in subtle ways, such that novel compounds are not registered and thus not always illegal. Legislation cannot keep up with this nefarious activity and new counter-crime measures and changes to the law are needed to counter the now enormous problems of 'legal highs'. If a compound is illegal, the possessor is liable for criminal proceedings even if sold as 'legal'.

Currently around 40–50 new drugs appear each year. Examples of this rapid rise include: 2006–2007, piperazines; 2008, spice/'K2'; 2009, cathinones – methedrone; 2010–2011, pipadrel, indanes, synthetic cocaines. Broadly, drugs may be stimulants ('highs'), depressants or hallucinogens/psychodelics (Table 2.74). Increasingly mixed activity is seen with newer drugs such as ketamine analogues (methoxetamine causes ketamine dissociation and

Table 2.74 Drugs of misuse and novel recreational drugs

Type of drug	Examples	What they are	What they do
Stimulants	Cocaine – crack (in ascending order of faster brain entry, worse effects and addiction: coca leaves, coca paste, cocaine, crack) Amphetamine – methamphetamine MDMA or 'ecstasy' Piperazines, e.g. BZP MDMA–BZP Catathiones – keto derivatives of amphetamine, e.g. mephedrone and 40+ others that include MDMA Amino-indanes / tetralins Synthetic cocaines	All are really amphetamines, based on phenylethylamine, and mimic brain excitatory neurotransmitters, e.g. GHB-GBL / 1,4-butanediol promotes dopamine release and action at GABA A and B receptors	Tachycardia, hypertension, palpitations Anxiety Headache Chest pain and myocardial infarction or stroke (norepinephrine-induced vasospasm) Dilated pupils Vomiting Tremor Agitation, delusions, paranoia Seizures Hepatitis (MDMA) Hyperthermia (especially MDMA with dancing) Hyponatraemia (MDMA) Withdrawal (depression and 'pseudo-Parkinsonism') Chronic frontal lobe damage
Depressants	Alcohol Opioids (in ascending order of faster brain entry, worse effects and addiction: codeine, opium, morphine, heroin, snorted heroin, intravenous / smoked heroin) Benzodiazepines – barbiturates GHB-GBL or 1,4-butanediol Ketamine (K, special K, super K, ketalar, green)	Morphine is the compound which exerts effects in the brain via opioid receptors, and codeine and heroin are hydrophilic and lipophilic pro-drugs, respectively, with respective slow and fast effects Ketamine is an antagonist at *N*-methyl-D-aspartate receptors	Respiratory depression, enhanced if multiple substances taken (e.g. drugs with alcohol) Depression Dissociation and catatonia (ketamine) Delirium (especially ketamine taken to 'come down' after cocaine) Hypothermia Opioid withdrawal (tremors, shivering, crying, diarrhoea, pain) Chronic bladder damage and urinary problems (ketamine)
Hallucinogens	Cannabis LSD–psilocybin (mushrooms) Salvinorum Glaucine TFMPP Spice / K2 (synthetic cannabinoid receptor agonist) Tryptamines Mitragnice	Hallucinogenic	Perhaps less physically risky than other drugs except that they induce people to do silly things such as jumping off buildings Anxiety Acute psychosis Some are also stimulants

BZP, benzylpiperazine; GABA, γ-aminobutyric acid; GHB-gbl, Gamma-hydroxybutyric acid-gammabutyrolactone; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; TFMPP, 3-trifluoromethylphenylpiperazine.

catatonia effects with additional stimulant and neuropsychiatric effects) and an array of 'designer' medications that may have stimulant and profound hallucinogenic neuropsychiatric effects such as etaqualone, methylmetaqualone and *o*-desmethytramadol (o-Dt).

Treatment

The vast range of neurotransmitters stimulated or inhibited by drugs offers the potential to modify drug effect with counteractive therapeutic agents, for example naloxone for opiates, flumazenil for benzodiazepines, and haloperidol for cocaine. However, it is increasingly difficult to know what has been taken and a quiet room, time and benzodiazepines, if needed, are mainstays of treatment.

Haematological problems

CASE 2.32 ANAEMIA

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr Jim Case, aged 82 years

Thank you for seeing this gentleman with a haemoglobin of 8.2 g/dl. He has complained of several episodes of feeling tired and light-headed over the past 6 months and his haemoglobin a year ago was 11.5 g/dl. His current renal function is normal. His blood pressure is satisfactory. He had a sigmoid resection 4 years ago for colorectal cancer and no longer appears to be under surveillance for this and I wonder if he requires repeat colonoscopy and exclusion of other causes of anaemia.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Jim Case is an 82-year-old man who for the last 12 months has felt increasingly tired and weak, and on occasion dizzy, although he has never passed out. His wife died a year ago, and since then he has been eating very little. He never cooks, and manages for the most part on 'cereal and toast'. He and his wife used to enjoy an active social life, and half a bottle of wine daily each was typical. Now he drinks closer to a bottle. He has hitherto been a generally well and active man. Four years ago he had an operation to remove part of the bowel for a malignant polyp but was subsequently given 'the all clear'. He has had no bleeding per rectum (the mode of presentation of his bowel problem 4 years ago) and no other gastrointestinal symptoms. He has lost around 5 kg in weight. He takes aspirin (some years ago he was told it might be protective against bowel cancer) but no other drugs. He misses his wife dreadfully and sees life without her as bleak. He is now not too concerned about recurrence of bowel cancer; he would consider investigation for causes of anaemia, but only because his grandchildren make life tolerable.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

■ **Consider possible causes.** Ask about possible sources of blood loss, especially rectal bleeding, dyspepsia and alarm symptoms. In females you would always ask about menorrhagia or vaginal bleeding.

■ **Ask about symptoms.**

- Ask about fatigue, pre-syncope or breathlessness.
- Very severe anaemia (not the case here) of any cause may cause high-output cardiac failure.
- Megaloblastosis may occur outside the bloodstream; overt subacute combined degeneration of the cord is rare, but there may be paraesthesia and impaired vibration sense.
- Marrow infiltration of any cause can cause leucopenia (sepsis) and thrombocytopenia (petechiae).

Patient perspective

Try to establish why he has presented now, his thoughts about what his symptoms and anaemia might represent, and his keenness or otherwise for investigation. Here, keep closely in mind that bereavement and depression are likely to be playing a key role.

Past medical history

The history of colorectal cancer may be relevant. Ask about possible malabsorption symptoms such as diarrhoea or steatorrhoea (Crohn's disease, coeliac disease) and any history of autoimmune disease or gastrectomy (vitamin B12 deficiency).

Drug and allergy history

Ask about drugs that can provoke gastrointestinal bleeding, e.g. aspirin, non-steroidal anti-inflammatory drugs, warfarin.

Family history

Relevance here is unlikely.

Social history

Dwell considerably on this. Discover why he has been drinking more and eating less and the impact of his bereavement on his feelings of social isolation and loneliness. Find out what, if any, support structures he currently has (family, friends, neighbours) and whether or not he goes out any more.

Discussion

What is anaemia?

This refers to low haemoglobin concentration, which may occur if haemoglobin synthesis fails or if red blood cells are prematurely destroyed.

What are the general signs of anaemia?

There is pallor of conjunctival membranes, buccal membranes, palmar creases and nail beds. Iron deficiency anaemia may produce ridged brittle nails, koilonychia or spoon-shaped nails, angular stomatitis and dysphagia. Megaloblastic anaemia may produce atrophic glossitis. Haemolytic anaemia can lead to jaundice.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ Possible causes of anaemia include recurrence of colorectal cancer, aspirin-induced gastritis or ulcers, and dietary deficiency.
- ◆ He should have a full examination, including digital rectal examination.
- ◆ Investigations should include estimation of his red cell parameters, haematinics (ferritin, folate, vitamin B12), and a biochemical profile including liver function. Ferritin might be raised in malignancy, hiding iron deficiency. Faecal occult blood testing is generally of no value other than in population screening.
- ◆ Colonoscopy and oesophagogastroduodenoscopy with duodenal biopsy should almost certainly be offered to him. The British Society of Gastroenterologists recommends that all iron deficiency requires oesophagogastroduodenoscopy and colonoscopy (computed tomography in frail elderly may be a reasonable substitute); sigmoidoscopy is insufficient. Sometimes small-bowel-related iron deficiency anaemia (e.g. coeliac disease, covert Crohn's dieace, angio-ectatic disease) is to blame.
- ◆ Transfusion (not least because of its known and unknown potential risks, e.g. West Nile virus, new variant Creutzfeldt–Jakob disease, Simian foamy virus) is now only considered if patients are markedly symptomatic or the haemoglobin is around 8 g/dl or less; it should not be considered in megaloblastosis.
- ◆ Other possible contributors to anaemia could include myelodysplasia, anaemia of chronic disease (although no suggestion here) or non-gastrointestinal malignancy, notably renal cell carcinoma.
- ◆ His bereavement and depression warrant specific, specialist help.

What do you know about iron uptake, transport and storage?

An average diet contains 15 mg of daily iron, of which 1 mg is absorbed from the duodenum and jejunum, increasing to a maximum of 3–4 mg in deficiency. The *HFE* gene product (abnormal in genetic haemochromatosis) is one protein responsible for its uptake. Iron is transported in plasma bound to transferrin, and cells requiring iron express receptors to which transferrin delivers its iron. In iron deficiency, the number of transferrin receptors, and hence total iron-binding capacity, increases. Iron is stored in the liver and reticuloendothelial system, and incorporated into haemoglobin in the bone marrow.

What are the causes of microcytic anaemia and how would you differentiate iron deficiency anaemia from other causes of microcytic anaemia and other anaemais with altered iron status?

Microcytic anaemias are:

- Iron deficiency anaemia
- Thalassaemia
- Sideroblastic anaemia (failure of iron incorporation in cells leading to defective erythropoiesis).

Altered iron status may occur in anaemia of chronic disease as well as iron deficiency anaemia.

Serum iron status markers, peripheral blood film and bone marrow aspirate findings for these various anaemias are shown in Table 2.75.

How is sideroblastic anaemia treated?

If there is no reversible cause (e.g. myelodysplasia), folic acid 5 mg daily may counteract ineffective erythropoiesis. Transfusion is often required, and desferrioxamine may be needed in iron overload.

What is anaemia of chronic disease?

This occurs in a wide variety of inflammatory, infectious and neoplastic disorders but the severity of the anaemia does not correlate with the severity of the underlying systemic disease. Anaemia is initially normochromic and normocytic but tends to become hypochromic and microcytic with time, when small molecules like hepcidin involved in the pathogenesis inhibit iron absorption and inhibit iron release from macrophages. Since ferritin tends to be raised in inflammatory disease, the transferrin receptor assay is useful in identifying iron deficiency. Recombinant human erythropoietin and erythropoietin stimulating agents, commonly used in chronic kidney disease, are probably underused in malignancy-related anaemia and could reduce blood transfusion.

List some causes of normochromic–normocytic anaemia

- Chronic disease
- Chronic kidney disease (anaemia of chronic disease as well as reduced erythropoietin) – irregular, spiky red blood cells called echinocytes or Burr cells sometimes seen
- Pregnancy
- Bone marrow failure

What is megaloblastic anaemia?

Megaloblastic anaemia is characterised by macrocytosis and megaloblastic erythropoiesis. The common denominator is faulty DNA synthesis resulting from deficiency of vitamin B12 or folate. It is occasionally the result of drugs inhibiting metabolism, e.g. azathioprine, aciclovir, hydroxyurea.

List some conditions that can cause macrocytosis

- Megaloblastosis (B12 or folate deficiency)
- Haemolysis or acute blood loss (abundant reticulocytes of larger diameter)
- Liver disease, especially alcohol, which alters red cell membrane lipids

Table 2.75 Differentiating microcytic anaemias and other anaemias with altered iron status

	Iron deficiency	Thalassaemia trait	Sideroblastic anaemia	Anaemia of chronic disease
Causes	Blood loss Dietary deficiency	Genetic	Acquired, e.g. myelodysplasia, lead poisoning Congenital	Systemic inflammatory disease
Peripheral blood film				
MCV (normal 78–100 fl) and MCH	Microcytic and hypochromic (defective haemoglobinisation)	Marked microcytosis	Typically dimorphic with small population of microcytic, hypochromic red cells Mild macrocytosis usual in elderly Anaemia may be severe	Normochromic and normocytic initially Microcytic and hypochromic later
Other	Sometimes elongated pencil cells Occasional target cells (ring of pallor due to defective haemoglobinsation) ↑ red cell distribution width – a measure of MCV uniformity	Basophilic stippling (RNA remains in cells with defective Hb) sometimes seen in thalassaemias and lead poisoning	Pancytopenia confers poor prognosis in myelodysplasia – high risk of transformation to acute myeloid leukaemia	Other anaemias often coexist altering the picture, e.g. iron deficiency
Serum iron status markers				
Serum iron	↓	Normal/↑	↑	↓
Transferrin / total iron-binding capacity	↑	Normal	Normal	↓
Transferrin saturation	↓	Normal/↑	↑	↓
Ferritin	↓ (may be if ↑ concurrent inflammation)	Normal/↑	↑	Normal / ↑
Soluble transferrin receptor assay	↑	Normal	Normal	Normal
Bone marrow				
Bone marrow erythroblast iron stores (Perls' stain)	↓ or absent stores and absent siderotic granules with normal cellularity	Normal/↑	↓	Normal / ↑
Sideroblasts	↓ / absent	Present	Ring sideroblasts as a result of failure to incorporate iron into haemoglobin	Absent

Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume.

- Hypothyroidism
- Pregnancy
- Myelodysplasia (dyserythropoiesis)

List some causes of vitamin B12 or folate deficiency

These are listed in Table 2.76.

What abnormalities may appear on a megaloblastic peripheral blood film?

Oval macrocytes and hypersegmented neutrophils (more than five lobes to the nucleus) are common. Bone marrow examination is seldom necessary with vitamin B12 and folate assays but would show increased cellularity, loss of fat spaces and accumulation of precursor cells – erythroid precursors, 'giant' metamyelocytes and megaloblasts. At all stages nuclei are primitive with an open 'lacy' chromatin pattern.

What is 'pernicious' anaemia?

This is the most common cause of vitamin B12 deficiency, caused by autoimmune gastritis with parietal cell destruction. Gastric parietal cell antibodies are present in 90% and intrinsic factor antibodies in 50%, the latter being more specific.

Table 2.76 Causes of B12 and folate deficiency

B12 deficiency	Folate deficiency
Inadequate intake	**Inadequate intake**
Vegan	Elderly Alcohol
Intrinsic factor deficiency	**Malabsorption**
Pernicious anaemia (autoimmune) Gastrectomy	Coeliac disease Tropical sprue
Small intestinal disease	**Small bowel disease**
	Increased utilisation or loss
Bacterial overgrowth (blind or 'stagnant' loops) Crohn's disease / terminal ileum resection Coeliac disease Tropical sprue Miscellaneous (human immunodeficiency virus drugs: metformin proton pump inhibitors)	Pregnancy Haemolysis Myelofibrosis Malignancy Severe inflammation (exfoliative skin disease, Crohn's disease) Liver failure, heart failure Homocystinuria
	Drugs
	Methotrexate (inhibits dihydrofolate reductase) Anti-epileptics: valproate, phenytoin Trimethoprim
Pancreatic deficiency	

What are the complications of B12 deficiency?

Megaloblastosis can cause multi-system effects, notably cardiomyopathy and neurological disease, e.g. subacute combined degeneration of cord, peripheral neuropathy, dementia.

How would you treat B12 deficiency?

Hydroxycobalamin 1 mg intramuscularly on alternate days for 2 weeks, then 3-monthly may be a reasonable replacement regimen.

Is there a risk in administering a blood transfusion in the setting of B12 deficiency?

Severe vitamin B12 deficiency with megaloblastosis and a high lactate dehydrogenase (cells lyse easily) is dangerous. Transfusion is not necessary in pure B12 deficiency. In mixed anaemia with severe B12 deficiency, B12 should always be replaced before transfusion because transfusion can precipitate heart failure (megaloblastic cardiomyopathy) or provoke an aplastic crisis.

Are there risks in giving folate in the setting of B12 deficiency?

Giving folate in severe vitamin B12 deficiency can precipitate neurological problems. Vitamin B12 and folate (and ferritin because stores are often used up in B12 deficiency) may be given together, but B12 replacement should never be 'second'.

Is red cell folate a better marker of tissue folate status than serum folate?

Yes.

If both folate and iron levels are low, what condition would you screen for?

Coeliac disease. Indeed, coeliac disease is now one of the commonest causes of isolated iron deficiency.

What is haemolytic anaemia?

Haemolysis refers to destruction of peripheral red cells earlier than their normal life span of 120 days. Anaemia occurs if the marrow response fails to compensate. Most causes of haemolysis are extravascular (cells destroyed in the reticuloendothelial system, e.g. spleen), an accentuation of the normal destruction process. Some causes are intravascular, leading to red cell fragmentation being observed on the blood film.

What are the laboratory findings in haemolytic anaemia?

- Unconjugated hyperbilirubinaemia (jaundice is common)
- Increased urinary urobilinogen
- Reduced or absent serum haptoglobins
- Increased serum lactate dehydrogenase
- Reticulocytosis
- Bone marrow erythroid hyperplasia
- Polychromasia

What is reticulocytosis?

Young red cells, normally constituting < 1% of cells in the periphery, are 'churned out' when erythropoiesis is increased to compensate for peripheral destruction (acute blood loss or haemolysis). A blue tinge to the blood film, polychromasia, is seen in reticulocytosis because the ratio of nuclear remnant material to haemoglobin is high.

When might you suspect a haemolysed blood sample?

If there is raised potassium, lactate dehydrogenase and phosphate in a patient in whom you do not suspect cell lysis for any reason, e.g. post chemotherapy.

What are the causes of haemolytic anaemia?

These are listed in Table 2.77.

Table 2.77 Causes of haemolytic anaemia

Extrinsic RBC abnormality (acquired)	Intrinsic RBC abnormality (inherited)
Antibody mediated	**Membrane abnormality**
Blood group incompatibility Autoimmune haemolytic anaemia	Hereditary spherocytosis / elliptocytosis
Non-antibody-mediated (tend to be intravascular)	**Metabolic enzymopathies**
*RBC fragmentation (DIC / TTP / HUS, severe hypertension or renal failure, prosthetic valve) Infection (*Mycoplasma pneumoniae*, Epstein–Barr virus, *Clostridium welchii*, *Plasmodium falciparum*) Drugs Paroxysmal nocturnal haemoglobinuria March haemoglobinuria	Glucose-6-phosphate dehydrogenase deficiency – by far most common Pyruvate kinase deficiency
	Haemoglobin abnormality
	Abnormal Hb structure (HbS – sickle cell disease, HbC, HbE) Abnormal Hb rate of synthesis (thalassaemias)

DIC / TTP /HUS, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome; Hb, haemoglobin; RBC, red blood cell.
*Microangiopathic haemolytic anaemia arises in these conditions, owing to splicing of red cells into fragments (or schistocytes, referred to as 'helmets' if cut in half) as a result of clumping of platelets in small vessels in DIC / TTP / HUS, endothelial damage in severe hypertension and physical attack from prosthetic valves.

How is autoimmune haemolytic anaemia (AIHA) detected?

The direct antiglobulin test, detecting antibodies on the red cell surface, is usually positive. In this test, the autoantibody coating the surface of red blood cells is detected directly by application of an antiglobulin.

What types of AIHA are there?

Warm AIHA, in which the autoantibody reacts best at 37 °C, may be idiopathic or secondary, e.g. systemic lupus erythematosus, lymphoproliferative disorders. There is often marked spherocytosis. Cold AIHA, in which the autoantibody reacts best at < 37 °C, may occur in infections such as *Mycoplasma* and infectious mononucleosis.

How would you treat AIHA?

If there is no identifiable cause in warm AIHA, prednisolone 1 mg/kg is given for 4 weeks or until haemoglobin is 12 g/dl, then reduced slowly. Splenectomy may be needed if there is no remission because red cells coated with immunoglobulin G are preferentially destroyed in the spleen (if complement coated then mostly in the liver, and testing for this may predict the value of splenectomy). Folic acid supplementation is given as for all chronic haemolytic anaemias. Blood transfusion may be needed. Immune suppression may be considered for refractory haemolysis with non-selective agents such as azathioprine, cyclophosphamide or ciclosporin A. Rituximab (anti-CD20 on B lymphocytes and plasma cells) may be effective. Plasma exchange remains controversial. Intravenous immunoglobulin is usually less successful than in autoimmune thrombocytic purpura.

List some other autoimmune cytopenias

- Autoimmune neutropenia
- Autoimmune thrombocytopenia (immune thrombocytopenic purpura)
- Autoimmune pancytopenia

What is schistocytosis?

This refers to the presence of fragmented red cells, seen in intravascular haemolysis, often as part of microangiopathic haemolytic anaemia. Strands of fibrin are laid down in small vessels and red cells are chopped into half (helmet cells) or multiple irregular fragments as they gush through.

What is paroxysmal nocturnal haemoglobinuria?

This is a rare condition in which the red blood cell membrane is abnormally sensitive to complement lysis because of aberrant membrane-anchored proteins which normally inhibit lysis. It can cause mesenteric thrombosis. Transfusion and anticoagulation may be needed.

What are Howell–Jolly bodies?

These are nuclear remnants normally removed by the spleen, hence present post splenectomy and in hyposplenic states such as coeliac and sickle cell disease.

What is aplastic anaemia?

This is pancytopenia due to marrow hypoplasia, which may be idiopathic or a consequence of drugs (e.g. chloramphenicol, gold), chemicals or infection, e.g. parvovirus B19.

What is myelodysplasia?

The myelodysplastic syndromes are discussed in Case 1.45.

How might you manage pancytopenia of any cause?

As well as identifying and correcting any correctable cause, supportive care with blood and platelet transfusion and granulocyte colony-stimulating factor is often needed. Broad-spectrum antimicrobial therapy (e.g. tazocin, gentamicin) is needed in possible neutropenic sepsis.

CASE 2.33 SICKLE CELL DISEASE AND THALASSAEMIA

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr James Beech, aged 22 years
> Thank you for admitting Mr Beech, who has sickle cell disease and new abdominal pain. He frequently requires admission with his symptoms.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr James Beech is a 22-year-old medical student with sickle cell anaemia. He has been admitted to the emergency ward again with abdominal pain. He was only here a month ago and is frustrated because his fourth year examinations are pending. Past problems have included mild growth problems, recurrent abdominal pain, painful fingers (now with some deformities that limit his ability to write) and priapism. He does not smoke but does drink alcohol in binges close to examination time, not least because he feels annoyed that he has to work harder than his colleagues because of his condition; he knows that alcohol can precipitate sickling crises but is determined to lead as normal a life as possible and drinks plenty of water to try to compensate for his alcohol intake.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

- **Evaluate symptoms.** Take a thorough history of possible symptoms in sickle cell disease (SCD) (Box 2.85).

Patient perspective

Dwell considerably on this. Discover how he has been managing at medical school so far and what support structures he currently has (family, friends, mentors). Establish the difficulties posed by the unpredictability of symptoms, not least on his study and examinations.

Past medical history

Establish the range of hospital admissions he has endured before.

Drug and allergy history

Ask about prescription and non-prescription drugs.

Family history

This is very relevant.

Social history

Establish details about his drinking and its effects on symptoms.

SUMMARY BOX – ASSESSMENT AND PLAN

- The diagnosis is probably not really in doubt, but remember that other causes of abdominal pain such as appendicitis are of course possible.
- The peripheral blood film in sickle cell anaemia is likely to reveal anaemia (haemoglobin 6–10 g/dl), reticulocytosis, target cells, and Howell–Jolly bodies due to autosplenectomy; definitive diagnosis requires haemoglobin electrophoresis.
- Treatment of a sickling crisis includes oxygen, hydration, analgesia and antibiotics. Numerous therapies are being evaluated which may reduce polymerisation.
- Appropriate psychological support may need to be sought in the longer term.
- Asplenic individuals should be vaccinated against *Pneumococcus*, *Meningococcus* and *Haemophilus*.

Box 2.85 **Clinical consequences of severe sickle cell disease (SCD)**

Anaemia

The most common causes are transient red cell aplasia (often associated with *parvovirus B19*), acute splenic sequestration, and hyperhaemolysis in patients with severe infection; haemolysis occurs because red cells fail to negotiate tight capillaries resulting in anaemia, jaundice and a predisposition to pigment gallstones.

Pain from vaso-occlusive crises

Acute painful episodes account for more than 90% of hospital admissions in adults. Pain is the hallmark of SCD, arising as sickle cells impede blood flow. Dactylitis (digits of various lengths, deformed, often active finger swelling) is a common early manifestation. Abdominal pain is common, often associated with splenic sequestration. Severe disease causes autosplenectomy, but milder forms may cause splenic sequestration without infarction and the spleen may be palpable because of 'congestion', often associated with hyposplenism, and elevated white cell and platelet counts. Exposure to cold, fever and dehydration shorten the time for haemoglobin S to polymerise and increase the risk of vaso-occlusive episodes.

Infection

Infections by encapsulated bacteria such as pneumococcus occur in part because recurrent splenic infarction decreases the ability of the spleen to clear circulating antigens. The risk of overwhelming infection is highest in early childhood. Other common infective complications include meningitis–septicaemia and osteomyelitis (often *Salmonella*).

Acute chest syndrome

This occurs in around half of all patients at some stage. It refers to a new pulmonary infiltrate on the chest radiograph combined with one or more manifestations such as fever, cough, sputum production, tachypnoea, dyspnoea, or new onset hypoxia. It may be due to infection, but commonly is due to infarcts in adults.

Pulmonary hypertension

This occurs in about 30% of adults with SCD and strongly predicts mortality. It is associated with a haemolytic phenotype (low haemoglobin and raised lactate dehydrogenase levels) and high rates of leg ulceration, priapism, and chronic kidney disease.

Stroke

This occurs in 11% of patients with SCD by age 20 years.

Priapism

These may be brief but recurrent or may last for hours.

Chronic organ damage

Vaso-occlusion, hyperhaemolysis, and increased blood viscosity are major determinants of chronic organ damage (aseptic osteonecrosis – especially of the humeral and femoral heads, chronic kidney disease due to impaired renal tubule concentrating ability and papillary necrosis, leg ulceration and retinopathy), which varies widely in severity among patients.

Discussion

How might abnormalities in red cell components give rise to inherited anaemia?

Red cells are approximately 8 µm wide and biconcave with an area of central pallor. Their size and shape enable them to squeeze through capillaries, with normally only minimal anisocytosis (variation in size) and poikilocytosis (variation in shape). Any of the three components of a red cell – membrane, enzymes and haemoglobin – may lead to anaemia if at fault.

Hereditary spherocytosis and abnormalities of the red cell membrane

The membrane bears blood group antigens and comprises a lipid bilayer and underlying protein skeleton. Alterations in its lipid can cause macrocytosis without anaemia. Alterations in cytoskeletal molecules (e.g. spectrin) can cause haemolysis. In hereditary spherocytosis abnormal membrane proteins render the red cell excessively permeable to sodium influx. Some of the membrane is spliced in the spleen to leave small spherical cells without central pallor (spherocytes). Ultimately, spherocytes are haemolysed in the reticuloendothelial system. Osmotic fragility tests reveal increased susceptibility to lysis compared with normal red blood cells. Splenectomy is often needed.

Enzymopathies

The metabolic energy-creating pathways are the Embden–Meyerhof pathway and the hexose monophosphate shunt. Energy is used to maintain osmotic stability by membrane pumps. Enzymopathies within these metabolic pathways cause haemolytic anaemia. Heinz bodies are inclusions of oxidised haemoglobin seen in glucose-6-phosphate dehydrogenase deficiency.

Haemoglobinopathies – SCD and thalassaemias

Normal haemoglobin (Hb) comprises four haem groups (as a tetramer) and globin. Each haem group is an oxygen-binding site. Normal adult haemoglobin (HbA, α_2, β_2) comprises two α- and two β-globin polypeptide chains, with a trace of HbA_2 (α_2, δ_2) and sometimes a trace of fetal Hb (α_2, γ_2). In the haemoglobinopathies, abnormal polypeptide chains are produced (SCD) or normal polypeptide chains are produced in decreased amounts (thalassaemias).

What is the underlying abnormality in SCD?

SCD is an autosomal recessive disease producing a structural abnormality in haemoglobin. Valine is substituted for glutamine at position 6 on the β-globin chain, giving rise to the haemoglobin S (HbS) gene. Sickle cell haemoglobin (HbS) molecules derived from this gene tend to polymerise. The rate of polymerisation is accelerated by hypoxia, an increased concentration of intracellular haemoglobin or a decreased concentration of fetal haemoglobin (HbF). Polymerisation renders the red blood cell less pliable and it distorts into its characteristic sickle shape. Sickle cells have a reduced deformability and are easily destroyed and chronic haemolytic anaemia is a prominent manifestation of SCD. In addition to HbS polymerisation, key pathophysiological features of the disease include adhesion of young red cells to venular endothelium, chronic inflammation, ischaemia reperfusion injury leading to endothelial damage, and dysregulated nitric oxide homeostasis. Although most people with the disease live in Africa, where the sickle mutation appeared several thousand years ago, SCD has become common in the USA and Europe since the migration of African people.

What types of SCD are there?

Clinical severity has extreme phenotypic variability: a minority have few complications and disease is clinically unapparent; a majority have intermediate forms; and another minority have severe complications including sepsis, strokes, recurrent painful episodes, acute chest syndrome, pulmonary hypertension and priapism. Interaction of environmental factors with genetic polymorphisms is the most likely reason.

The spectrum of SCD is shown in Table 2.78. Homozygosity for the HbS allele (haemoglobin SS disease) is the most common finding, but some patients are heterozygous for HbS and for another haemoglobin mutation such as HbC (haemoglobin SC disease) or β-thalassaemia ($S\beta^0$ and $S\beta^+$ diseases).

Table 2.78 The sickling spectrum

Homozygous (SS) sickle cell anaemia	This occurs when HbS is inherited from both parents, and it tends to be severe.
Heterozygote (AS) sickle cell trait	Inheritance of the HbS gene from one parent and a normal β-globin gene from the other results in this harmless carrier state.
Sickle cell / haemoglobin C (SC) disease	This occurs if HbS is inherited from one parent and HbC from the other. The HbC gene is the second commonest haemoglobin gene abnormality in West Africa. HbSC disease tends to be mild but important microvascular complications can occur.
Sickle cell / thalassaemia	This is designated β^+ if 20–30% of HbA (normal adult haemoblobin) is present and β° if no HbA is present. β^+ tends to be mild clinically but β° is severe.

How is SCD diagnosed?

In western Europe and the USA, it is diagnosed by neonatal screening. Haemoglobin electrophoresis identifies variant haemoglobins, possibly combined.

How can complications of SCD be prevented and treated?

Pain

Effective treatment of acute pain is one of the most common and challenging problems in SCD, and involves seeking the cause as well as effective analgesia, often with opiates. Hydroxycarbamide may help prevent recurrences of painful crises in severe SCD; it acts in part by reactivating the synthesis of HbF, which inhibits the polymerisation of HbS. It is licensed in the USA in adults with recurrent moderate to severe painful crises (at least three episodes over 12 months) and in Europe in adults and children with recurrent vaso-occlusive events.

Preventing infection

Pneumococcal immunisation as well as prophylactic penicillin is recommended, together with annual influenza vaccination.

Acute chest syndrome

Antibiotics are given routinely, and the high rate of atypical micro-organisms requires combination of a macrolide with intravenous cephalosporin. Transfusion or exchange transfusion has produced improvements in several uncontrolled studies.

Pulmonary hypertension

There is no proved treatment. Regular blood transfusions or long-term anticoagulation are often suggested, and other treatments as for primary pulmonary hypertension are being explored.

Stroke

Transcranial Doppler ultrasonography is performed annually in children aged 2–16 years with SCD with regular blood transfusions strongly considered in those with abnormal findings. Experts agree that exchange transfusion should be performed when a stroke occurs, since more than half of patients with a first stroke have another and long-term observational studies show that monthly transfusions decrease the risk of recurrent stroke.

Priapism

Priapism is an emergency requiring intravenous hydration and analgesia.

What are the risks of general anaesthesia in SCD?

The complications of SCD often require surgery, e.g. cholecystectomy, hip replacement and splenectomy. However, patients with SCD are at high risk of perioperative complications, mainly acute chest syndrome and pain, which probably relate to hypoxia, hypoventilation and hypothermia.

What are the risks in pregnancy in SCD?

Worsening anaemia, vaso-occlusive crises and acute chest syndrome may occur during pregnancy, and fetuses are at risk of prematurity, low birth weight or even death.

What are the thalassaemias and how do they arise?

The thalassaemias are a group of autosomal recessively inherited conditions caused by an inefficient rate of synthesis of one or more globin chains (compared with SCD in which normal globin chains are not produced). This leads to underproduction of haemoglobin and an imbalance in globin chain synthesis. The chains that are produced in excess precipitate, and formation of rigid inclusions (Heinz bodies) leads to premature cell destruction (haemolytic anaemia).

Depending upon which pair of globin chains, α or β, has inefficient production, α-thalassaemias or β-thalassaemias result. The α-thalassaemias are more common than β-thalassaemias. Thalassaemias are most common in people of Far and Middle Eastern origin, and global migration has resulted in wider dispersal of people at risk of thalassaemia.

What types of α-thalassaemia are there and how are they diagnosed?

There are two α-genes on each chromosome such that normal individuals have four copies of the α-gene (unlike just two copies of the β-gene). There are four possible genetic abnormalities (Table 2.79).

What types of β-thalassaemia are there?

β-thalassaemias are common in people of Mediterranean, Middle and Far Eastern origin, and over 180 different mutations of the gene have been described which decrease the output of β-globin chains, either completely or partially. There is just one β-gene on each chromosome such that normal individuals have only two copies of the β-gene (unlike four copies of the α-gene). There are two common genetic abnormalities, β-thalassaemia minor and β-thalassaemia major (Table 2.80).

How are patients with thalassaemia treated?

Asymptomatic carriers

Carriers require no specific treatment but should be protected from detrimental iron supplementation given merely on the basis of microcytosis. Iron supplementation should be given only after confirmation of iron deficiency.

Thalassaemia intermedia

Patients with thalassaemia intermedia or haemoglobin H disease need to be closely monitored for progression of complications induced by chronic haemolytic anaemia. Symptoms usually develop when the haemoglobin level is sustained at below 70 g/l. Occasional blood transfusion may be required. Indications for transfusion include:

- Haemoglobin concentration < 50 g/l
- Falling haemoglobin level with profound enlargement of the spleen
- Growth failure
- Diminished exercise tolerance
- Severe bone changes
- Pregnancy
- Infection

Table 2.79 Types of α-thalassaemia and diagnostic features

Type	Genotype	High-performance liquid chromatography	Phenotype
Deletion of one gene		Normal	Asymptomatic carrier state with a normal blood film, possibly with borderline microcytic anaemia and hypochromia
α^{+}-thalassaemia, heterozygous	–α / αα		
Deletion of two genes		Normal	Asymptomatic thalassaemia trait with mild hypochromic, microcytic anaemia
α^{+}-thalassaemia, homozygous	–α / –α		
α^{0}-thalassaemia, heterozygous	– / αα		
Deletion of three genes		HbH	Anaemia (haemoglobin 7–10 g / dl) and splenomegaly. The reduced rate of α-chain synthesis generally leads to an excess of β- and γ-chains, and the presence of 'golf ball cells' on the blood film reflects precipitation of β-globin chains in the red cell
HbH disease	– / –α		
Deletion of all four genes		Hb Bart's	Severe, non-immune intrauterine haemolytic anaemia Hydrops fetalis and stillbirth
α^{-}-thalassaemia major	– / –		

Table 2.80 Types of β-thalassaemia and diagnostic features

Type	Genotype	High-performance liquid chromatography	Phenotype
β-thalassaemia trait / minor	$- / \beta$	$HbA_2 > 4\%$ HbA present	May be mildly anaemic during times of stress but otherwise have merely a hypochromic, microcytic blood film
β-thalassaemia intermedia (can result from different complex combinations)	$- / \beta^0$ or β^+ / β^+	High HbF, variable HbA	Anaemia Marked microcytosis and hypochromia Splenomegaly Variable bone changes Variable transfusion dependency
β-thalassaemia major	$-^0 / -^0$	HbF > 90% (untransfused) No HbA	Severe anaemia (Hb 2–8 g / dl) from deficiency of β-chains; compensatory excess of α-chains, which damage red cells A blood film showing severe hypochromia and microcytosis, target cells and reticulocytosis Extramedullary haemopoiesis and hepatosplenomegaly Hypertrophy of ineffective marrow leading to bone expansion and skeletal abnormalities Failure to thrive, almost inevitable A need for repeated blood transfusions which downregulate marrow dyserythropoiesis but lead to secondary haemochromatosis

Hb, haemoglobin; HbA, normal adult haemoglobin; HbF, fetal haemoglobin.

- Other specific complications: heart failure, pulmonary complications, hypertension, thromboembolic disease, leg ulcers, priapism.

If hypersplenism develops, splenectomy may be considered, although it carries severe risks of life-threatening infections, pulmonary hypertension and thrombosis.

Thalassaemia major

The Thalassaemia International Federation has published guidelines for the clinical management of thalassaemia major. The cornerstones of treatment are:

- Regular hypertransfusion to maintain a haemoglobin level higher than 95 g/l
- Iron chelation to prevent overload syndrome
- Care by a multidisciplinary team (haematologist, specialist nurse, social worker, psychologist, genetic counseller, cardiologist and hepatologist) with endocrinological, skeletal, hepatic and cardiac monitoring.

Splenectomy for hypersplenism may be needed. Patients receiving optimal transfusion and chelation from an early age have substantially increased survival of more than 40 years. Hypertransfusion decreases autogenous, ineffective erythropoiesis and haemolytic anaemia. However, an adverse effect of this treatment is iron overload, because each unit of red blood cells adds 200 mg of iron, which can only be slowly removed from the body. The complications of iron overload are cardiomyopathy and liver cirrhosis. Furthermore, transfusional iron overload affects endocrine organs (hypothalamus, pituitary, gonads, pancreas, thyroid and parathyroid glands). Cardiac failure is the most common fatal complication in patients with thalassaemia major treated with chronic transfusion. The risk of transmission of viral infections (human immunodeficiency virus, hepatitis B, and hepatitis C) remains a serious problem in many countries. To reduce the risk of alloimmunisation, extended red blood cell antigen phenotyping before transfusions is needed. It is important to evaluate iron concentration and function in the heart and liver since the prediction of iron loading (especially cardiac iron) from serum ferritin can be unreliable. Iron concentration in the liver can be determined by biopsy and non-invasive methods are based on magnetic resonance imaging (MRI). Compromised left ventricular ejection fraction is a late sign of cardiomyopathy and not of use in the prevention and early detection of cardiac iron overload but estimation of myocardial iron with MRI may be used. Iron overload should be treated when serum ferritin levels exceed 1000 μg/l, which will occur after 10–20 red cell transfusions. Treatments include deferoxamine subcutaneous infusion promoting urinary and faecal iron excretion, the oral chelator deferiprone promoting urinary iron excretion and oral deferasirox promoting faecal iron excretion.

Alternative therapeutic options

Splenectomy can be considered if hypersplenism causes a marked increase in transfusion requirements but in general should be delayed for as long as possible in order to prevent life-threatening infections, pulmonary hypertension and thromboembolic complications.

Hydroxyurea, a cytotoxic drug, may increase the expression of γ-chains (HbF) and enables the neutralisation of excess α-chains, potentially correcting ineffective erythropoiesis.

Potential cure

The only potential cure for β-thalassaemia is haematopoietic stem cell transplantation.

CASE 2.34 PURPURA

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Megan May, aged 35 years

Thank you for admitting Mrs May with a 5-day history of an evolving purpuric rash. She does not appear to have any bleeding from anywhere. Her blood count is as follows: haemoglobin 11.5 g/dl, white cell count 8.0 × 10^9 / l with a normal differential and platelets 15 × 10^9/l. She is usually very well and takes no medications.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Megan May is a 35-year-old woman who works as a writer for a national magazine. For the last few days she has noticed a gradually increasing purpuric, non-blanching rash which started in her hands but which now involves her arms, legs and trunk. The spots are flat, and many of them are tiny dots. She feels otherwise well. She has not experienced epistaxis, bleeding gums or bleeding from any other site. She has no headache or fever. There is no lymphadenopathy. There is no history of any recent viral illness. There are no unwell contacts. She lives with her husband and two children. Her last menstrual period was a week ago and a little heavier than usual. She does not smoke or drink alcohol. She has mild asthma for which she has an occasional Ventolin inhaler. She does not take any regular medications other than the contraceptive pill and has not recently taken any tablets such as antibiotics or corticosteroids. She is clearly concerned about the rash.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Establish purpura details.** Establish the duration of symptoms, the distribution of the rash, and its features (Table 2.81).

■ **Ask specific questions.** Ask specifically about:

- Fever
- Joint pains (Henoch–Schönlein purpura)
- Lymphadenopathy
- Recent viral symptoms.

Patient perspective

Address her understandable concerns by sharing the possibilities. It is probably not wise to mention malignancy at this stage as a possibility unless she asks, but if so then to share that it seems unlikely with a severe but isolated drop in the platelet count.

Past medical history

Ask about any history of lymphoproliferative disease.

Drug and allergy history

Ask about prescription and non-prescription drugs. Drugs notorious for causing thrombocytopenia include

Table 2.81 Features of purpura (bruising) that help distinguish a platelet problem from a coagulopathy

	Platelet problem	Coagulopathy
Sites of bleeding	Mucosal – epistaxis, genitourinary, gastrointestinal	Muscle and joint Visceral and intracranial bleeds potentially life threatening
Precipitating factor	Spontaneously or with minimal trauma	Spontaneously or with minimal trauma
Characteristic signs	Petechiae (representing small endothelial lesions that have failed to heal)	Haemarthroses Joint deformity ultimately Excessive bleeding from small cuts not typical since platelet activation, adhesion and aggregation are sufficient to seal small endothelial lesions; haemostasis of larger wounds requires fibrin reinforcement relying on effective coagulation

sulphonamides and chloramphenicol, and corticosteroids can cause purpura.

Family history

Ensure there are no unwell contacts.

Social history

Ask about alcohol intake. Human immunodeficiency virus risk factors are important to exclude/establish.

SUMMARY BOX – ASSESSMENT AND PLAN

- This is a typical presentation of idiopathic/autoimmune thrombocytopenic purpura (ITP). Other possibilities are drug-induced thrombocytopenia, infection (e.g. toxoplasmosis, cytomegalovirus, Epstein–Barr virus), bone marrow failure (e.g. leukaemia, metastatic malignancy or infiltration) or a coagulopathy.
- In ITP the blood count reveals isolated thrombocytopenia. Serology for infectious causes (including human immunodeficiency virus if risk factors) should be requested, together with an autoimmune profile, although in ITP platelet autoantibodies are generally unreliable. Bone marrow examination is often important to exclude other causes.
- Treatment of ITP is with corticosteroids (with concomitant bone protection) but in rare, serious cases intravenous immunoglobulin may have a role.
- Splenectomy is usually reserved for cases that are refractory to other measures.
- Alemtuzumab (anti-CD52 on T and B lymphocytes) may be effective in refractory cases, but not rituximab (anti-CD20 on B lymphocytes), emphasising the importance of T cells in ITP (unlike autoimmune haemolytic anaemia in which rituximab may be effective).

Discussion

How is haemostasis regulated?

A tightly regulated homeostatic mechanism involving the endothelium, platelets, coagulation and fibrinolysis maintains physiological blood flow but permits rapid, localised thrombus formation at sites of tissue damage.

How does the endothelium contribute to haemostatic homeostasis? (Fig. 2.11A)

The endothelial surface normally inhibits thrombus formation. A negative charge repels platelets, ectoenzymes degrade platelet agonists such as adenosine diphosphate (ADP), the vasodilators nitric oxide and prostacyclin inhibit platelet adhesion and aggregation, and surface expression of thrombomodulin and heparan sulphate enhance anticoagulation.

With tissue damage, blood vessels constrict and the subendothelial extracellular matrix is exposed. Exposed collagen (types I and III), von Willebrand factor (vWF) and fibronectin promote platelet adhesion. Cytokines (interleukin-1, tumour necrosis factor, interferon-γ) or endotoxin render damaged endothelium prothrombotic. Tissue factor (TF) is expressed, which initiates the coagulation pathway, plasminogen activator inhibitor is secreted to impair fibrinolysis and thrombomodulin expression is reduced.

The endothelium is not just dynamic but is heterogeneous, leading to the modern concept of vascular-bed-specific haemostasis. Discrete thrombotic episodes are typical, and the ability of a vascular bed to compensate depends upon the local antithrombotic–prothrombotic seesaw.

Box 2.86 **Vascular disorders that cause purpura**

- Age-related purpura
- Corticosteroid-induced purpura
- Vasculitis
- Henoch–Schönlein purpura (an immunoglobulin A vasculitis affecting skin, joints and gastrointestinal tract, with immunoglobulin A nephropathy)
- Scurvy
- Infection (viral, bacterial, e.g. meningococcal septicaemia)
- Hereditary causes (hereditary haemorrhagic telangiectasia, Ehlers–Danlos syndrome, osteogenesis imperfecta, Marfan's syndrome)

List some vascular disorders that cause purpura

These are listed in Box 2.86.

How do platelets contribute to thrombus formation? (Fig. 2.11B)

Platelets normally circulate in close contact with the endothelium, but adhesion is prevented by local nitric oxide and prostacyclin.

Platelet adhesion

With endothelial damage, platelet adhesion occurs rapidly between platelets and exposed subendothelium. Blood flow is faster at the centre of vessels than close to the endothelium, creating shear effects between adjacent layers of blood that are highest nearer the endothelium. In high-flow conditions, platelets adhere to the subendothelium by the interaction of their glycoprotein (Gp) 1b receptors with vWF present on the subendothelium, and in low-flow conditions platelets adhere to the subendothelium by the interaction of their GpIaIIb receptors with other endothelial material, largely collagen.

vWF is a large, multimeric protein synthesised by the endothelium and secreted into the subendothelium. After endothelial damage it binds to extracellular collagen, primarily through its A3-binding site. The Gp1b–IX–V complex binds to the A1-binding site of vWF despite high flow because of a high association rate. However, a concurrent high dissociation rate allows platelets to roll slowly along the endothelium.

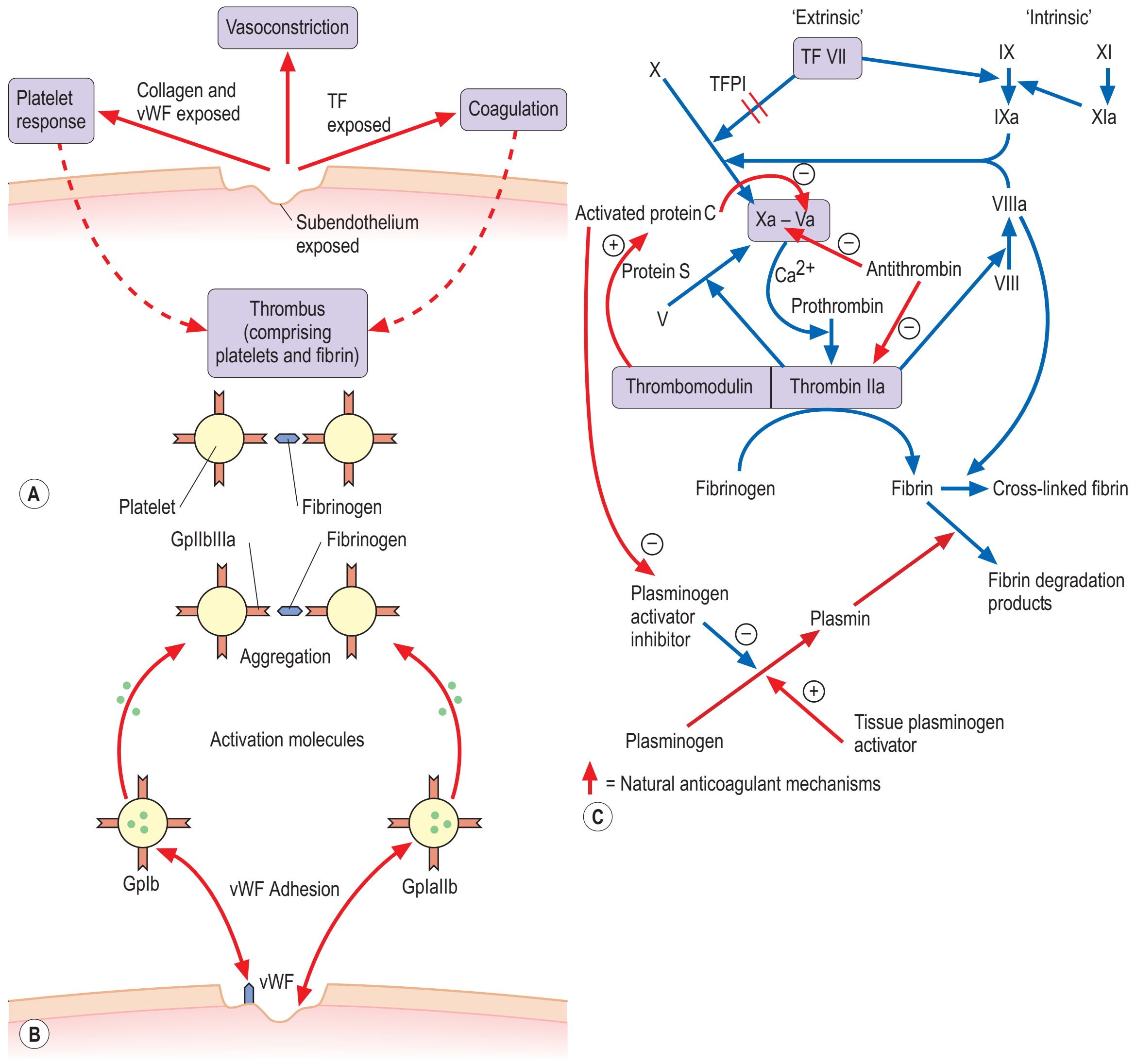

Vasoconstriction
Platelet response
Collagen and vWF exposed
TF exposed
Coagulation
Subendothelium exposed
Thrombus (comprising platelets and fibrin)
A
Platelet
Fibrinogen
GpIIbIIIa
Fibrinogen
Aggregation
Activation molecules
GpIb
vWF Adhesion
GpIaIIb
vWF
B
'Extrinsic'
'Intrinsic'
TF VII
X
TFPI
IX
XI
IXa
XIa
VIIIa
Activated protein C
Xa – Va
Protein S
V
Ca2+
Antithrombin
Prothrombin
VIII
Thrombomodulin
Thrombin IIa
Fibrinogen
Fibrin
Cross-linked fibrin
Fibrin degradation products
Plasminogen activator inhibitor
Plasmin
Plasminogen
Tissue plasminogen activator
= Natural anticoagulant mechanisms
C

Figure 2.11 Haemostatic homeostasis: (A) endothelial response to bleeding; (B) platelet adhesion, activation and aggregation; (C) coagulation. Gp, glycoprotein; TF, tissue factor; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor.

Platelet activation

Platelet activation occurs during the rolling phase and is the result of the binding of various agonists (e.g. thromboxane A_2, collagen, ADP, thrombin, arachidonic acid) to specific receptors leading to intracellular changes including reduced adenylate cyclase activity and cAMP, calcium mobilisation and secretion of platelet granules.

Platelet aggregation

During activation the platelet GpIIbIIIa receptor undergoes a conformational change, allowing it to bind to the dimeric fibrinogen molecule, and irreversible platelet aggregation occurs.

How do antiplatelet agents work?

These agents are described in Case 2.9 (Acute coronary syndrome).

List some platelet disorders that cause a bleeding tendency

These are listed in Table 2.82.

What is idiopathic thrombocytopenic purpura?

This commonly affects women between 20 and 40 years of age. It may present acutely with an abrupt fall in platelet

Table 2.82 Platelet disorders that cause a bleeding tendency

Decreased bone marrow production	Myelodysplasia Aplasia, e.g. drugs, chemicals, radiation or infection (e.g. *parvovirus B19*) Bone marrow infiltration, e.g. leukaemia, metastatic disease, tuberculosis Myelofibrosis Drugs, including alcohol Vitamin deficiency (B12 or folate) Congenital disorders, e.g. May–Hegglin anomaly, Bernard Soulier syndrome, Wiskott–Aldrich syndrome, Fanconi's anaemia, thrombocytopenia–absent radii syndrome
Increased peripheral destruction	Immune causes, e.g. drugs, infections, HIV, ITP, SLE or other autoimmune disorders, post transfusion Disseminated intravascular coagulation Thrombotic thrombocytopenic purpura Hypersplenism
Platelet dysfunction	Renal failure Congenital, e.g. Glanzmann's disease with GpIIbIIIa receptor deficiency (rare)

Spontaneous bleeding seldom occurs until the platelet count is $< 20 \times 10^9$ / l.

HIV, human immunodeficiency virus; ITP, idiopathic thrombocytopenic purpura; SLE, systemic lupus erythematosus.

count, or can be a chronic, relapsing condition. There is often a history of easy bruising or menorrhagia. Autoantibodies directed against platelet glycoproteins lead to autoantibody–platelet complexes that are then sequestered in the spleen, but the trigger to this autoimmunity is usually unclear.

What are the thrombotic microangiopathies?

These are described in Box 2.87.

At what level of thrombocytopenia does purpura start to appear?

Purpura (petechial) is unusual spontaneously if normally functioning platelets are above 10×10^9 to 20×10^9 / l, but may occur after injury at higher levels.

Do you know of any recent advances in the understanding of blood coagulation (Fig. 2.11C)?

The coagulation 'jigsaw'

The traditional concept of intrinsic and extrinsic pathways failed to explain why factor XII deficiency does not cause bleeding despite its supposed role in initiating the intrinsic pathway, why factor XI deficiency causes only a mild bleeding tendency, why factor VIII and IX deficiencies cause severe bleeding, but theoretically should be bypassed by factor VII activity, and why thrombus generation *in vitro* has a lag phase. The two-pathway concept is being superseded with recognition of the tissue factor–factor VII complex (TF.VII) as central to coagulation. The puzzle is less of a sequence and more of a jigsaw.

Box 2.87 **The thrombotic microangiopathies**

These are a group of conditions characterised by microvascular thrombosis, microangiopathic haemolytic anaemia and thrombocytopenia. Renal involvement, due to occlusion of glomerular capillaries and renal arterioles by platelet–fibrin thrombi, is a common though not universal finding.

Haemolytic uraemic syndrome (HUS)

HUS has prominent renal involvement and is classified into two major subtypes. Diarrhoeal HUS (D+ HUS) is associated with a preceding diarrhoeal illness, commonly caused by *Escherichia coli* O157:H7. Atypical HUS (aHUS) is associated with mutations in proteins of the alternative pathway of complement, particularly complement factor H. Plasma exchange is the mainstay of treatment for aHUS.

Thrombotic thrombocytopenic purpura (TTP)

TTP has prominent microvascular neurological effects (usually confusion) and is caused by an inherited or acquired deficiency of the von Willebrand factor (vWF)-cleaving metalloprotease, ADAMTS13, that normally degrades ultra-large multimers of vWF to smaller vWF proteins; this leads to enhanced platelet–vWF adhesion, enhanced platelet aggregation and microangiopathic haemolysis. Plasma exchange is the mainstay of treatment.

Disseminated intravascular coagulation (DIC)

DIC is the enhanced and abnormally sustained generation of thrombin triggered by inflammatory mediators, usually in severe sepsis. It is characterised by anaemia, thrombocytopenia, raised prothrombin time and partial thromboplastin times, decreased fibrinogen and raised D-dimer levels. These lead to microthrombus deposition which can result in acute kidney injury, acute respiratory distress syndrome, skin necrosis / purpura fulminans / gangrene, and organ failure such as liver failure, heart failure and adrenal failure. Treatment is of the cause, with supportive therapy and replacement of missing factors such as fresh frozen plasma, platelets and cryoprecipitate.

The central role of TF and factor VIIa

TF is expressed on fibroblasts but may be induced by endotoxin, interleukin-1 and tumour necrosis factor in other cells, including endothelial cells. TF is only fully active in a damaged environment and subendothelial exposure causes factor VII or activated factor VII (VIIa) to bind to TF. Activation of VII to VIIa may be by autoactivation of the TF.VII complex, but trace amounts of Xa may aid activation and small amounts of basal VIIa are present (which are reduced in factor IX deficiency).

Why factor Xa is so important

Activated factor Xa is generated by TF.VII and stimulates sufficient amounts of factor IIa (thrombin) to induce local platelet aggregation and activation of the critical cofactors V and VIII. This is insufficient to sustain haemostasis because of rapid Xa inactivation by TF pathway inhibitor. Instead, marked amplification of Xa is facilitated by factors IXa and VIIIa. Factor XIa may be needed to generate additional factor IXa. Factor XI activation may involve thrombin. Much about coagulation remains unknown but the remaining pieces of the intrinsic jigsaw seem not to be important in haemostasis and relevant only *in vitro*.

Not forgetting factor Va and the prothrombinase complex

The prothrombinase or tenase complex (factor Xa–Va), incorporating Va, which is crucial to Xa's activity, rapidly converts prothrombin (II) to thrombin (IIa).

And finally, the importance of thrombin

Thrombin converts soluble fibrinogen to insoluble fibrin, activates factor XIII, which stabilises the fibrin clot, and has positive feedback on coagulation by activating factors in the intrinsic pathway (including factor XI) and factor V.

Natural anticoagulation mechanisms

Procoagulation is itself regulated, to prevent unhindered thrombosis, by mechanisms that include:

- Thrombin binding to endothelial *thrombomodulin* (which on binding to thrombin activates *protein C* in the presence of its *cofactor protein S* rendering *activated protein C able to cleave and inactivate factor V* and the other cofactors)
- *Antithrombin* binding to and inactivation of thrombin and Xa; antithrombin is one of several 'serpins' that inhibit clotting proteases, including the recently discovered protein Z-dependent protease inhibitor
- *Tissue plasminogen activator* secretion by endothelial cells.

List some coagulation disorders that cause a bleeding tendency

These are listed in Table 2.83.

Table 2.83 Coagulation disorders that cause a bleeding tendency

Congenital disorders	Haemophilia A and B von Willebrand disease Factor XI deficiency Deficiencies of all other coagulation factors described but rare
Acquired disorders	Anticoagulant drugs Vitamin K deficiency Liver disease Disseminated intravascular coagulation Acquired factor inhibitors

CASE 2.35 HAEMOPHILIA

Patient information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Nick Adler, aged 39 years
> Thank you for seeing this gentleman with haemophilia who has had some bleeding today following a fall onto his knee. Although mild there is a steady leak from a laceration to his leg and the knee joint to me looks a little swollen.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Nick Adler is a 39-year-old man with haemophlia A and a usual factor VIII level of around 10% of normal. This tends to result in continuous bleeding after mild to moderate trauma. Today he fell onto his left knee off a bicycle and sustained a laceration to it that is continuing to ooze after 6 hours of pressure. He has therefore been admitted to hospital. His knee joint is swollen but he has had multiple previous haemarthroses of both knees and the left is usually a little more deformed and swollen than the right. He does not have pain. He has no history of intracranial bleeding and did not bang his head on this occasion. He is otherwise well but does carry the hepatitis C virus as a result of blood transfusions many years ago. He does not have human immunodeficiency virus infection. He is married, without children. He has come to terms with his condition very well, and sees a liver specialist 6-monthly for monitoring of what is currently inactive hepatitis C. He works as a computer graphics designer. He is well informed about haemophilia and feels he will need factor VIII replacement on this occasion.

Table 2.84 Severity of haemophilia

Factor level (%)	Clinical defect
> 50	Normal
20–50	Abnormal bleeding after severe trauma
5–20	Abnormal bleeding after mild trauma
2–5	Abnormal bleeding after trivial trauma/ occasional spontaneous bleeding
< 2	Spontaneous bleeding into joints, muscles and soft tissues

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem/s and symptom exploration

■ **Evaluate symptoms.** Haemophilia typically causes joint and muscle bleeding and symptom severity depends significantly on the factor level (Table 2.84).

■ **Explore risks and complications.** As well as blood transfusion risks, the significant problems of haemophilia relate to joint damage and comprehensive assessments often involve a haematologist, rheumatologist, orthopaedic surgeon and physiotherapist. Intracranial haemorrhage and visceral bleeds can occur with minimal trauma and are an important source of morbidity and mortality.

Patient perspective

Discover what he knows about his condition. He is probably more likely than most doctors to know if he has sustained a haemarthrosis and what will be needed on this occasion to stem the bleeding.

Past medical history

Explore the risk consequences of previous blood transfusions.

Drug and allergy history

He is likely to know which drugs to avoid in haemophilia.

Family history

The mode of haemophilia A and B inheritance is X-linked, such that all males carrying the affected X chromosome will have haemophilia and all females are carriers (unless, rarely, she is the daughter of a haemophilia male and carrier female). Carrier females may exhibit mild disease if factor production is sufficiently impaired. Around half of sons of carriers have haemophilia and half of daughters are carriers. The severity of disease tends to be similar between generations.

Social history

Establish if he is doing all that he can (within the limits of his wishes) to minimise injuries. Presumably the cycling was not competitive racing?

SUMMARY BOX– ASSESSMENT AND PLAN

- You would arrange for baseline blood tests including an urgent haemoglobin and ensure that blood is available in the event that transfusion were absolutely necessary.
- You would liaise with his haematology team and arrange treatment, probably in the form of recombinant factor VIII.
- You would consult the orthopaedic team if you felt he had a significant haemarthrosis.

Discussion

What are the commonest haemophilias?

Haemophilia A and B are the commonest inherited coagulopathies but are rare (1 : 10 000). Haemophilia A (deficiency of factor VIII : C) is about five times more common than haemophilia B (deficiency of factor IX). Rarer deficiencies have been described for all clotting factors.

How might laboratory investigations be useful in haemophilia?

The activated partial thromboplastin time (APTT) is usually prolonged ('intrinsic' pathway) but the prothrombin time (tissue factor or 'extrinsic' pathway) is normal. APTT corrects with the addition of normal plasma in a 50 : 50 mix in inherited haemophilia but not in the less common acquired factor VIII disease where there is an inhibitor (autoantibody) against factor VIII. Specific assays demonstrate reduced factor VIII : C or IX levels.

How is bleeding in haemophilia managed?

A normal bleeding time is less than 10 minutes. In haemophilia continuous bleeding often occurs, or becomes apparent hours or days after injury. Replacement of the missing factor is the key to therapy, freeze-dried factors from large donor pools historically used but gradually being replaced by recombinant factors. A formula for dosage is:

$$\text{Factor replacement} = \%\ \text{increase in factor required}$$

Factors have only a short half-life (8–12 hours for VIII and 12–24 hours for IX) *in vivo*.

Desmopressin (DDAVP/synthetic antidiuretic hormone) combined with an antifibrinolytic agent increases factor VIII levels in patients with mild haemophilia A. Antifibrinolytic agents have been combined with factor concentrates for external bleeding but not usually with factor IX because of the risk of thrombosis or in haematuria because of risks of clot retention.

What is von Willebrand disease (vWD)?

This is caused by mutations in the von Willebrand factor (vWF) gene on chromosome 12, resulting in quantitative or qualitative abnormalities in vWF. vWF is synthesised in endothelial cells (to an extent bone marrow) and acts as a subendothelial binding protein for platelets via GP1b and as a carrier molecule for factor VIII in the bloodstream to sites of vascular injury. There are three types of vWD:

1. Type 1 (70% of cases, autosomal dominant) is a partial quantitative deficiency of vWF, with a propensity to mucocutaneous bleeding (epistaxis, menorrhagia). Laboratory findings are reduced levels of vWF antigen (protein) and activity (by ristocetin cofactor or RCo assay) with normal or increased ristocetin-induced platelet aggregation (RIPA), which measures sensitivity of ristocetin-induced interaction of the patient's vWF with their own platelets.
2. Type 2 has four subtypes:
    - Type 2A mutations result in a failure of vWF multimer assembly (group 1) or increased sensitivity to degradation by the vWF cleavage protease ADAMTS13 (group 2), resulting in loss of circulating high- and medium-molecular-weight multimers, with a corresponding low-vWF antigen level and disproportionately lower RCo level.
    - Type 2B is a mutation of the platelet GP1b binding site that results in higher affinity of vWF for GP1b, so that vWF binds spontaneously to platelets in the circulation, causing loss of high-molecular-weight circulating multimers, with a corresponding low-vWF antigen level and disproportionately lower RCo level.
    - Type 2M results in decreased affinity for the GP1b receptor. There is a corresponding low-vWF antigen level and disproportionately lower RCo, and markedly reduced RIPA activity. Multimer analysis reveals a full set of multimers.
    - Type 2N (autosomal recessive) results in decreased affinity for the factor VIII binding site. Factor VIII levels in homozygotes may be in single figures; vWF antigen and activity levels, RIPA and multimer studies are normal.
3. Type 3 (5% of cases) is caused by two null vWF genes, with no detectable vWF antigen or activity levels, absent RIPA activity and no detectable multimers; factor VIII levels are also low (prolonged APTT) and bleeding is of haemophilia and mucocutaneous type.

Treatment for all types may be with factor VIII concentrate containing vWF, or in types 1, 2A and 2B desmopressin.

CASE 2.36 DEEP VEIN THROMBOSIS

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Esther Summers, aged 60 years
> Thank you for seeing this lady with a short history of leg swelling and breathlessness. She had a mastectomy for breast cancer 2 years ago and a perioperative DVT and I am concerned that this is further venous thromboembolism.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Esther Summers is a 60-year-old woman with right-sided calf and leg swelling for the last 3 days. She usually has mild swelling of both legs but this does not unduly trouble her and she has been talking a small dose of furosemide for a couple of years on an occasional basis. She has also been more breathless in the last week. She does not have chest pain or other cardiorespiratory symptoms. She has a history of breast cancer with a mastectomy and axillary clearance 2 years ago and takes tamoxifen. She is not taking any other medications. She does not smoke. She recently visited her sister in the USA, returning 2 weeks ago. She is a widow, and is currently caring for one of her grandchildren. She is not particularly concerned about the possibility of another deep vein thrombosis (DVT).

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Evaluate symptoms.** Unilateral leg swelling represents a DVT until proven otherwise, unless an alternative such as cellulitis is very evident. Bilateral leg swelling may be the result of heart failure, nephrotic syndrome and other low-protein states, hypothyroidism or a saddle thrombosis (the last usually in the setting of malignancy).

■ **Consider risk factors for venous thromboembolism.** Risk factors include:

- Acute phase of illness
- Trauma, surgery
- Immobility/inactivity including long-haul flights
- Dehydration
- Pregnancy (oral contraceptive pill/hormone replacement therapy slightly increase risk)
- Obesity
- Malignancy, e.g. pancreas, prostate
- Myeloproliferative disorders and hyperviscosity syndromes
- Nephrotic syndrome
- Heart failure
- Antiphospholipid syndrome and hereditary thrombophilias
- Hyperhomocysteinaemia.

■ **Clinical model.** Post-test probability in venous thromboembolism (VTE) relates to pre-test clinical probability and the nature of the test, e.g. V/Q, computed tomographic pulmonary angiogram. Accurate diagnosis of DVT can be a challenge, and various clinical scoring systems are used including the (maximum) nine-point version of the Canadian Wells score for predicting pre-test probability for DVT (Table 2.85). Note that this differs from the Wells score used in diagnosing pulmonary embolus. Clinical intuition has a strong place for experienced physicians.

The Wells DVT score probably performs differently in different clinical settings, but clinical judgement still has final veto.

Table 2.85 Wells scoring system for predicting pre-test probability for deep vein thrombosis (DVT)

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilisation of legs	1
Recent bed rest for > 3 days or major surgery within 4 weeks	1
Localised tenderness along distribution of deep vein system	1
Entire leg swollen	1
Calf swelling by > 3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Previous documented DVT	1
Alternative diagnosis as or more likely than that of DVT	−2
	Low probability < 2
	High probability ≥ 2

Patient perspective

It is probably best to advise her that a DVT is likely but that you will need to confirm this with an ultrasound scan, and, if confirmed, consider whether or not the long-haul flight is enough to explain it, but that you think it would also be sensible to recheck things from the point of the breast cancer to make absolutely certain things are still all clear.

Past medical history

The history of breast cancer and DVT is highly relevant.

Drug and allergy history

Tamoxifen is not a contributor.

Family history

Establish any family history of blood clots.

Social history

Establish who will look after her grandchild while she is in hospital.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ Her risk factors for deep vein thrombosis (DVT) include previous DVT and previous malignancy, and a recent long-haul flight.
- ◆ The diagnosis should be established by ultrasound scan; it might be suggested by a D-dimer although here a negative D-dimer is not likely to dissuade you from further testing.
- ◆ Low-molecular-weight heparin is the initial treatment of choice for DVT and pulmonary embolism, with subsequent warfarinisation and if this proves to be recurrence of DVT then indefinite anticoagulation with warfarin is indicated.
- ◆ The possibility of recurrent malignancy should be explored.

Discussion

Where is a DVT usually located?

Distal veins in the leg are most common, followed by the femoral and popliteal veins and sometimes the iliac vein. Axillary vein thrombosis may occur.

What do you know about the role of D-dimer testing in suspected VTE? (Table 2.86)

Plasma D-dimers are specific cross-linked derivatives of fibrin (fibrin degradation products). They are sensitive but not specific for VTE and arise in many other situations including sepsis, trauma, surgery, pregnancy and post-partum. The usefulness also varies with age and comorbidity.

Does the absolute level of a positive D-dimer correlate with the likelihood or severity of the VTE?

No. There is no evidence that any value above the cut-off correlates with the likelihood of VTE. It may

Table 2.86 The role of D-dimer testing in suspected venous thromboembolism (VTE)

Pre-test probability of DVT / VTE	Likelihood of VTE on venography (gold standard) (%)	Likelihood of VTE with negative D-dimer (%)	Implications of D-dimer testing
High	75	21	D-dimer unhelpful because still need to ultrasound scan a 21% probability
Intermediate	17	1.8	Physicians might accept a 1.8% probability as sufficiently low to not test further, but the 1.8% figure relies on the more sensitive D-dimer assays
Low	3	0.3	D-dimer converts low to very low probability, i.e. no further testing needed

correlate with the size of the DVT, age or likelihood of malignancy.

How is a DVT treated?

After a first DVT or pulmonary embolism without ongoing risk factors, 3 months of anticoagulation is advised.

There is no evidence supporting 6 months of treatment. Daily wearing of compressive stockings for 2 years and immediate mobilisation are important. A second DVT or pulmonary embolism (or a first with ongoing risk factors) suggests a need for lifelong anticoagulation. Anticoagulation protects against pulmonary embolism but post-thrombotic syndrome is common after DVT.

What is post-thrombotic syndrome?

This is a chronic debilitating condition seen in about 43% of patients with DVT within 2 years. Patients present with a painful heavy leg and may also have cramps, paraesthesia and pruritus. Catheter-directed thrombolysis for DVT is a new treatment under study that may improve quality of life and reduce the risk of post-thrombotic syndrome.

What treatment is advised for VTE in pregnancy?

Low-molecular-weight heparin (LMWH) is safe and effective in the treatment and prophylaxis of VTE in pregnancy.

How does heparin work?

Heparin forms a high-affinity complex with antithrombin and accelerates its action. Antithrombin inactivates both thrombin (IIa) and Xa when it binds to these (Fig. 2.11C, Case 2.34), but the rate of inactivation is relatively low. Heparin strongly catalyses the action of antithrombin by inducing a conformational change in antithrombin within the heparin–antithrombin–thrombin complex leading to irreversible binding of antithrombin to thrombin. Heparin can interfere with diagnostic testing for antithrombin deficiency.

Unfractionated heparin (UFH)

UFH is a long molecule which complexes with antithrombin, causing it to bind with and accelerate the action of both coagulation factors. The anti-Xa : anti-IIa antithrombin binding ratio of UFH is 1 : 1.

Low-molecular-weight heparin (LMWH)

LMWH complexes with and accelerates mostly that region of antithrombin binding to Xa. In other words, LMWH exerts more effect on the proximal part of the coagulation pathway. This results in higher bioavailability, a longer half-life, and lower propensity to thrombocytopenia. There may also be a lower osteoporosis risk. Monitoring partial thromboplastin time is not required with LMWH. LMWHs are administered subcutaneously in the treatment and prophylaxis of DVTs, pulmonary emboli and acute coronary syndromes.

What is heparin-induced thrombocytopenia (HIT)?

This is induced by heparin–platelet factor 4 complexes. It is more likely with UFH than LMWH. It usually occurs in the first few days of heparin use but may occur up to around 14 days. Platelet levels often fall to below half their baseline, though extreme falls (to single figures) are rare. Bleeding is uncommon. Patients are at much greater risk of new thrombotic events (venous or arterial) or worsening thrombosis, and thus mortality is high if heparin is continued in the face of HIT. A 'HIT' screen to identify the heparin–platelet factor complexes should be undertaken and an alternative antithrombotic agent used.

How do warfarin and vitamin K antagonists work?

Warfarin inhibits the procoagulant factors II, VII, IX and X but also the anticoagulant protein C. Since the half-life of protein C is short, a procoagulant state may precede warfarin's anticoagulant effect. This is seldom clinically significant but may cause problems in patients with underlying protein C underactivity and is responsible for the phenomenon of warfarin-induced skin necrosis. It is also the reason that heparin should be continued at least until and probably for some days after the international normalised ratio (INR) is therapeutic in those starting warfarin for VTE. Warfarin can interfere with diagnostic testing for protein C and S deficiency.

How may anticoagulation be reversed?

Heparin can be reversed if absolutely necessary with protamine, although LMWH reversal is incomplete. Over-anticoagulation with warfarin may need no treatment (INR < 10 and no bleeding) or vitamin K; it can be reversed rapidly with a prothrombin complex concentrate (Beriplex) in a life-threatening bleed, the dose being proportional to the INR and administered with vitamin K.

Do you know of any new anticoagulants?

These include indirect thrombin inhibitors, direct thrombin inhibitors and direct Xa inhibitors.

Indirect thrombin inhibitors – fondaparinux

Fondaparinux is a synthetic form of the heparin pentasaccharide molecule responsible for binding and activating antithrombin, resulting in only anti-Xa effect. In contrast to heparins which also inactivate thrombin to varying degrees, fondaparinux has no direct effect on thrombin. Rather, by specifically targeting Xa, fondaparinux exerts its antithrombotic effect by inhibiting thrombin generation. It had similar indications to LMWH, but its use is limited by cost other than in acute coronary syndromes where it has been shown to be superior.

Direct thrombin inhibitors (DTIs)

DTIs bind directly to IIa (thrombin) and block its interactions by binding to one of its three domains – the active or catalytic site or two exosites. Exosite 1 is a dock for fibrin. Exosite 2 is the heparin-binding domain. As well as heparin's ability to act in the heparin–antithrombin–thrombin complex, heparin can bind to both exosite 2 and fibrin. Because both thrombin exosites are occupied within this fibrin–heparin–thrombin complex, thrombin's activity is relatively protected from inactivation by the heparin–antithrombin complex. Thus, heparins have less capacity to inhibit fibrin-bound thrombin, which appears detrimental. DTIs act independently of antithrombin, and can inhibit thrombin bound to fibrin or fibrin-degradation products. DTIs, by reducing thrombin-mediated activation of platelets, also have an antiplatelet effect. Bivalent DTIs (e.g. hirudin, bivalirudin, lepirudin) block the active site and exosite 1, and dissociate from thrombin, leaving a small amount of free active thrombin. Univalent DTIs (e.g. dabigatran) block only the active site and inactivate fibrin-bound thrombin. DTIs have had an uneven history, early agents discontinued because of concerns about liver toxicity. Dabigatran is an oral agent now used for stroke prevention in atrial fibrillation and treatment of VTE, with efficacy similar to warfarin.

Direct Xa inhibitors

Rivaroxaban is an oral agent that directly inhibits Xa and is used for VTE prophylaxis post-hip or knee surgery; it is also being considered for use in prevention and management of VTE more widely (approved for treating pulmonary embolus, but with concerns about reversibility limitations), atrial fibrillation and acute coronary syndromes. Other oral Xa inhibitors in development include apixaban and edoxaban. Danaparoid is an inhibitor of Xa and thrombin used post surgery.

Do you know of any roles of therapeutic activated protein C?

Intravenous infusion of activated protein C is administered in selected patients with severe sepsis and multi-organ failure.

CASE 2.37 THROMBOPHILIC TENDENCY

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr Edward Ferrars, aged 28 years

Thank you for seeing this gentleman who appears to have a family history of venous thromboembolism. He himself had an axillary deep vein thrombosis 2 years ago diagnosed in South East Asia but this was thought to be due to prolonged carriage of a rucksack. He was warfarinised for 6 months. He is a new patient to my surgery and at a routine medical examination he mentioned that a brother has just been diagnosed with a deep vein thrombosis. I wonder if you would consider thrombophilia testing and / or long-term anticoagulation.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Edward Ferrars is a healthy 28-year-old who 2 years ago had an axillary vein thrombosis while backpacking in Thailand. This was thought to have been caused by prolonged axillary pressure of the backpack in combination with severe dehydration. He has two siblings, one of whom has just had a deep vein thrombosis (DVT) diagnosed at a slightly older age than he, but without any obvious cause. His mother had a DVT during pregnancy. To his knowledge his grandparents died of strokes and heart attacks at reasonable ages although he thinks a grandmother might have had a DVT when she sustained a hip fracture. There is no family history of recurrent miscarriage. He takes no medications, and does not drink or smoke. He is concerned that there appears to be a family history of blood clots and wonders if there is anything he might do to reduce his risk, especially as he is a professional wind-surfer and takes frequent long-haul flights.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Ask about:

- The circumstances and robustness of the diagnosis of the axillary vein thrombosis (diagnosis likely because he was taking warfarin)
- Family history (below)
- His general health now with a full systematic enquiry.

The inherited thrombophilias are summarised in Box 2.88.

Patient perspective

His concerns are entirely understandable.

Past medical history

The history of an axillary vein thrombosis is highly relevant because this is unusual without a lesion obstructing axillary flow.

Drug and allergy history

Ask about prescription and non-prescription drugs, including anabolic steroids.

Family history

The family history of at least two first-degree relatives with venous thromboembolism (VTE) is significant, and almost certainly warrants further assessment (see Case 2.36). Particular features to elicit are the age of family members when they developed symptoms and whether or not there were any clear provocative factors.

Box 2.88 **Inherited thrombophilias**

The natural anticoagulants, some of which are shown in Fig. 2.11C (Case 2.34), are impaired in inherited thrombophilias.

Protein C and S deficiencies and activated protein C resistance

Protein C is activated by thrombomodulin, an endothelial molecule that complexes with thrombin in homeostatic response to coagulation. Activated protein C cleaves factors Va and VIIa to prevent untamed clotting. Protein C deficiency may be autosomal dominant or recessive, the latter causing problems at birth. Protein S is a cofactor for protein C and protein S deficiency may cause similar disturbance. Factor V Leiden is a mutated form of factor V that is resistant to the effects of protein C. This is the commonest inherited thrombophilia and is also known as activated protein C resistance.

Antithrombin deficiency

Antithrombin deficiency is autosomal dominant and similarly common.

Prothrombin gene variant

G to A transposition at position 20210 in the 3′ untranslated region leads to elevated levels of prothrombin.

Dysfibrinogenaemia

This is rare and associated with low plasma fibrinogen levels.

Hyperhomocysteinaemia

This is discussed below.

Social history

His active lifestyle may be protective although long-term anticoagulation could carry particular risks.

SUMMARY BOX – ASSESSMENT AND PLAN

- There is probably an inherited thrombophilia exerting a modestly increased risk of venous thromboembolism.
- His active lifestyle may be protective against blood clots except for the long-haul flights, which merit advice about adequate hydration and mobility.
- Long-term anticoagulation might be considered pending the results of a thrombophilia screen (below).

What do you understand by the term thrombophilia?

This refers to an inherited or acquired disorder of coagulation, with the potential for thromboembolism. The most important risk factors for VTE are a personal or family history, with an approximate 10-fold increased relative risk if there is a first-degree relative with a history of VTE. It has been difficult to quantify risk attributable to inherited thrombophilias, largely because these do not act alone but conspire with other factors. Thrombotic risk in factor V Leiden heterozygotes, for example, is increased

Table 2.87 Risk of venous thromboembolism (VTE) attributable to inherited thrombophilia

	Approximate increased risk (relative risk) of VTE	Prevalence in patients with VTE (%)	Prevalence in normal population (%)
Protein C deficiency (heterozygous)	3–15×	3	0.3
Protein S deficiency (heterozygous)	3–15×	3	2
Antithrombin deficiency (heterozygous)	25–50×	1	0.2
Heterozygous factor V Leiden mutation	5× (homozygous 10–80×)	25–50	5
Heterozygous prothrombin G20210A	1.5–4× (homozygous 5–15×)	6	2
Heterozygous combined factor V Leiden and prothrombin G20210A	20×		

dramatically by smoking and the oral contraceptive pill. Estimated increases in relative risk are given in Table 2.87.

How does hyperhomocysteinaemia lead to a prothrombotic tendency?

There are strong links between hyperhomocysteinaemia and occlusive vascular disease. The reasons are speculative, but homocysteine is atherogenic and causes oxidative damage to low-density lipoprotein. It may modify apolipoproteins, and is hypertensive, interfering with endothelium-derived relaxation factor. It also seems to downregulate anticoagulation, including protein C and thrombomodulin expression, and activate coagulants such as factor V.

How does hyperhomocysteinaemia arise?

The conversion of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF) through methylene-tetrahydrofolate reductase (MTHFR) is a crucial starting point for normal homocysteine metabolism and DNA synthesis. The 5-MTHF is converted to tetrahydrofolate (THF) by MTHF:homocysteine methyltransferase, generating a methyl group that is transferred to homocysteine, converting homocysteine to methionine. It is the THF that is crucial to DNA synthesis. This series of reactions, known as the remethylation pathway of homocysteine metabolism, is folate dependent.

The mutated C677T MTHFR, known as the thermolabile variant, in its heterozygous form, is associated with a moderate (20%) increase in serum homocysteine and a modestly increased risk of arterial and venous thrombosis. The prevalence varies between populations but in many Western countries may be around 15%. Homozygous polymorphism is rare, but promotes markedly elevated homocysteine levels and vascular risk.

Homocysteine is not metabolised exclusively to methionine. In the alternative transulphuration pathway it is metabolised to cysteine by the action of cystathione β-synthase. Mutations in cystathione β-synthase give rise to homocystinuria, in which homocysteine levels and thrombotic risk are very high.

Why is folate important?

The B vitamins, especially folate, may protect against vascular disease, birth defects (neural tube defects), recurrent pregnancy loss and cancer by lowering homocysteine or by epigenetic mechanisms (several mechanisms pivotal to genomic machinery are sensitive to B vitamin status).

Dietary methionine cannot provide all the methyl groups needed for cellular methylation reactions and so *de novo* production of methionine is important. Folate stabilises the *C677T* variant gene by preventing release of its flavin cofactor and, as MTHFR is a flavin protein, riboflavin (B2) supplements may also lower homocysteine.

Precursors to DNA are dependent upon a healthy MTHFR pathway with adequate folate. If folate is low, uracil misincorporation occurs, leading to breaks in DNA and a predisposition to cancer.

Is there a role for folic acid in cardiovascular disease prevention?

High homocysteine levels contribute to arterial and venous thrombosis. Some evidence (not without some contradictions) suggests that lowering homocysteine levels by 3 mol/l from current levels (achievable with folic acid 0.8 mg daily) reduces the risk of ischaemic heart disease by 16%, of stroke by 24% and of VTE by 25%, and that folate should be considered for primary or secondary prophylaxis in people at risk. Testing homocysteine levels may not be necessary to institute therapy because of the high rate of occurrence of hyperhomocysteinaemia in people with vascular disease.

Is folate supplementation a good idea for the general population?

Folate used in food fortification is not a natural coenzyme and the long-term effects of unmodified synthetic folate are unknown. Furthermore, there is an increasing tendency for clinicians to recommend 5 mg of folate daily, which is more than 10 times that needed to give maximal methylfolate concentrations.

Who should be considered for thrombophilia screening?

A normal thrombophilia screen does not exclude prothrombotic defects that may yet be discovered and cannot be assumed to imply 'normal' or 'no increased risk' in the future or in other family members. There is no evidence that identifying an abnormality influences the type of anticoagulant treatment, its intensity or its duration. Therefore, identifying a thrombophilia will not influence a patient's immediate treatment. Whether it may be of value in preventing further thrombosis and in counselling other family members, notably any family members contemplating pregnancy, is an area of uncertainty and possible indications for thrombophilia testing include:

- Patients with apparently spontaneous thrombosis, particularly if young or if pregnant, e.g. stroke at a young age without risk factors
- Patients with thrombosis at an unusual site, e.g. sagittal sinus thrombosis
- Patients with recurrent thrombosis
- Patients with VTE and a history of VTE in a first-degree relative
- Recurrent pregnancy loss
- Pre-pregnancy counslling.

What do you know about antiphospholipid syndrome (APS)?

APS was first described by Hughes (Hughes syndrome) in patients with systemic lupus erythematosus (SLE) and positive anticardiolipin antibodies, who presented with a clotting syndrome of arteries and veins. Females had a high risk of recurrent miscarriage and late fetal loss. It is under-recognised.

What it is

APS is a systemic autoimmune disorder characterised by arterial and venous thrombosis, adverse outcomes in pregnancy (for mother and fetus), and raised titres of antiphospholipid antibodies. It occurs in isolation (primary APS) in more than 50% of patients, but can be associated with other autoimmune diseases, SLE being the most common – 20–35% of patients with SLE develop secondary APS. The population prevalence of primary APS is estimated to be 0.5%. APS occurs mainly in young women of fertile age.

Classification

Classification criteria are outlined in Box 2.89.

A rare (< 1% of all APS, but often presents *de novo*) acute variant of APS – catastrophic APS – results in widespread thrombotic microangiopathy and multiple organ failure, typically affecting brain, kidneys, lungs and skin. Thrombocytopenia, microangiopathic haemolysis, schistocytes and activation of the coagulation system occur, and so thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, and disseminated intravascular coagulation are differential diagnoses. Mortality is high.

Box 2.89 **Classification criteria for antiphospholipid syndrome (APS)**

APS requires at least one of the clinical criteria and one of the laboratory criteria:

Clinical criteria

Vascular thrombosis

- One or more episodes of arterial, venous or small-vessel thrombosis in any tissue or organ

Morbidity in pregnancy

- One or more unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation
- One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia
- Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomical or hormonal abnormalities excluded and paternal and maternal chromosomal causes excluded

Laboratory criteria

- Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart
- Medium or high titre of immunoglobulin (Ig) G or IgM anticardiolipin antibody in serum or plasma on two or more occasions at least 12 weeks apart
- Medium or high titre of IgG or IgM anti-β_2 glycoprotein I antibody in serum or plasma on two or more occasions, a least 12 weeks apart

Antiphospholipid antibodies

Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed at plasma proteins that bind to phospholipids. Some such antibodies have a paradoxical effect on coagulation: *in vivo* they are associated with thrombosis, but *in vitro* they increase phospholipid-dependent clotting times, a phenomenon known as 'lupus anticoagulant' activity. The lupus anticoagulant assay is a functional assay based on a combination of several clotting tests. Two other antibodies useful for diagnosing antiphospholipid syndrome are anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies, both of which can be detected by enzyme-linked immunosorbent assays (ELISAs). Antiphospholipid antibodies are found in 1–5% of apparently healthy people, although persistent positivity is rare. The correlation between antiphospholipid antibody and clinical symptoms is variable. But lupus anticoagulant seems strongly associated with venous thrombosis and stroke in SLE and in the general population, and with fetal loss at greater than 10 weeks' gestation, and predicts venous thrombosis and fetal loss more strongly than anticardiolipin antibodies. The anticardiolipin ELISA has high sensitivity but low specificity. The relation between anti-β_2-glycoprotein I antibodies and clinical symptoms and the clinical relevance of isolated anti-β_2-glycoprotein I antibodies are uncertain. People with positivity for all three antibodies have a particularly high risk for pregnancy morbidity or thromboembolism.

How antiphospholipid antibodies might cause APS

The cause of the production of autoantibodies to phospholipid-binding proteins such as anti-β_2-glycoprotein I is unknown. Antiphospholipid antibodies affect the coagulation cascade and inflammation. In a process mediated by β_2-glycoprotein I, antiphospholipid antibodies bind to platelets and endothelial cells, activating endothelial cells and inducing a procoagulant state. Antibody binding also activates complement with recruitment of more inflammatory cells, and tissue factor, leading to endothelial damage and thrombosis. Although cerebral involvement is thought to be thrombotic antiphospholipid antibodies may have direct effects on nerves. Thrombosis in placental vasculature was thought to be the cause of adverse outcomes in pregnancy, but antiphospholipid antibodies may bind directly to trophoblast cells.

Presentation

The clinical features of antiphospholipid syndrome are diverse and can affect all organ systems:

- Venous thrombosis is more common than arterial thrombosis, especially DVT and pulmonary embolism.
- Other vessels such as renal, hepatic, subclavian and retinal veins, cerebral sinuses and vena cava are sometimes involved. The most common arterial thrombotic events are stroke and transient ischaemic attack. Recurrent thrombotic events are common.
- Cerebral and neurological involvement is common in APS – cerebral ischaemia, migraine, cognitive dysfunction, seizures, chorea, transverse myelitis, psychosis, depression and Guillain–Barré syndrome.
- The most common cardiac abnormality is non-bacterial thrombotic endocarditis, which may be complicated by stroke. There is also an increased risk of myocardial infarction.
- Thrombosis can occur anywhere in the renal vasculature.
- Haematological manifestations include thrombocytopenia and haemolytic anaemia.
- Skin symptoms include livedo reticularis.
- Maternal and fetal effects in pregnancy.

Whom to test for antiphospholipid antibodies

Indications for testing for antiphospholipid antibodies are as follows.

Thrombosis

- Arterial thrombosis before age 50
- Unprovoked venous thrombosis before the age of 50
- Recurrent thrombosis
- Thrombosis at an unusual site
- Both arterial and venous thrombosis
- Thrombotic microangiopathy of unknown cause

Obstetric problems

- One or more unexplained fetal loss after 10 weeks' gestation
- Unexplained severe intrauterine growth restriction
- Early or severe pre-eclampsia
- Three or more spontaneous miscarriages before 10 weeks' gestation

Systemic lupus erythematosus

- At baseline

Treatment

Antithrombotic agents are the mainstay of treatment.

- For a first episode of unprovoked venous thrombosis or thromboembolism associated with persistent positive antiphospholipid antibodies, long-term anticoagulation with vitamin K antagonists, such as warfarin, is recommended. If a reversible risk factor (e.g. surgery, immobilisation, oestrogen therapy, pregnancy) is reliably eliminated then indefinite anticoagulation may not be justified.
- There are insufficient data on treating arterial cerebral events and either long-term anticoagulation with warfarin or low-dose aspirin is advised.
- There are few data guiding obstetric management. Warfarin crosses the placenta and is teratogenic in the first trimester of pregnancy so low-molecular-weight heparins are the agents of choice for antenatal thromboprophylaxis.
- In patients with SLE and antiphospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss.
- Treatments for catastrophic APS include anticoagulation, high-dose corticosteroids and plasma exchange, with or without intravenous immunoglobulins.

CASE 2.38 MYELOMA

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Frank Boyd, aged 66 years
>
> Thank you for seeing this man, who 12 months ago was found to have a monoclonal paraprotein band on protein electrophoresis but was well at the time. He has no past medical history of note other than hypertension and stable chronic kidney disease with a creatinine of 150 μmol / l. For the last 6 months he has had intermittent watery diarrhoea, initially worse after new antihypertensive treatment was started but this has now been stopped and his blood pressure is now normal and without any postural drop. Coeliac antibodies are negative. However, repeat protein electrophoresis now shows two monoclonal bands, his plasma viscosity is 2.6 and his creatinine is 370 μmol / l. His serum potassium is 2.3 mmol / l with normal serum sodium. A skeletal survey is normal. I would appreciate your advice.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Frank Boyd is a 66-year-old with a 6-month history of intermittent watery diarrhoea. Episodes last for a few days, although he may be well for weeks in between. He thinks it all began after a blood pressure tablet was started, but this was stopped soon afterwards and the diarrhoea has continued. He has a history of high blood pressure going back some years and takes amlodipine and ramipril, although his GP has recently stopped the ramipril because of worsening kidney tests. Mr Boyd is aware that his GP also obtained an abnormal blood test 12 months ago that can sometimes indicate a blood disease called myeloma. He refused referral to a hospital specialist at the time because he was afraid of a diagnosis of 'cancer'. However, the more recent tests indicate a worsening of that abnormality. He is a retired aircraft mechanic, lives happily with his wife and has smoked heavily since teenage years until recently. He has not been overseas for 30 years and his wife is well.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Where confronted with a single problem you can delve deeply into its nuances. Here, you do not know which of the paraproteinaemia and hyperviscosity, the renal failure or the diarrhoea are more significant, whether they are equally important, whether they represent separate underlying pathologies or whether there is a unifying diagnosis. This case illustrates the importance of steering close to a standard history-taking framework. Ask particularly about:

- Symptoms of myeloma (Table 2.88)
- The nature of the diarrhoea
- Causes of renal failure (dehydration, symptoms of heart failure, renovascular risk factors, drugs, prostatic symptoms).

Patient perspective

Acknowledge and explore his earlier concerns about investigation.

Past medical history

His background kidney disease renders his kidneys more susceptible to threat from any new insult.

Drug and allergy history

The angiotensin-converting enzyme inhibitor might have been an important contributor to the renal failure.

Family history

Relevance here is unlikely.

Social history

This could be relevant, especially with respect to chronic infectious diarrhoea (overseas travel, unwell family members).

Discussion

What is myeloma?

Myeloma refers to a malignant clone of B-cell-derived plasma cells in the bone marrow producing high concentrations of one particular (monoclonal) immunoglobulin. In 80% of patients there is a paraprotein in the serum, usually immunoglobulin G (IgG) or IgA class, but the abnormal cells may also produce free light chains small enough for excursion through glomeruli and tubules and appear in the urine as Bence Jones proteins (BJPs). In 20% of patients free light chains are present only without paraprotein in serum but with BJPs in the urine. The serum free light chain (SFLC) immunoassay is a newer test that detects and measures light chains in serum. Rarely, the cell clone does not secrete immunoglobulin or light chains (non-secretory myeloma), but the SFLC test may reveal an M-protein in apparently non-secretory myeloma.

The clinical features of myeloma result from malignant plasma cells infiltrating bones or other organs (e.g. myelosuppression, hepatosplenomegaly), increased paraprotein levels (e.g. hyperviscosity symptoms, paraesthesia from peripheral neuropathy) or light chains in the serum (e.g. provoking light chain nephropathy).

Table 2.88 Clinical features of myeloma

Problem	Prevalence	How it arises	Symptoms
Bone disease	The most common presenting symptom (60% of patients)	Myeloma cells migrate from vessels and adhere to marrow stromal cells under the influence of cytokines; this causes stromal cells to produce IL-6, an important growth and survival factor for myeloma cells IL-1, IL-6 and TNF-α, increased in the myeloma milieu, mediate osteoclastic resorption through RANK-L whilst osteoprotegerin, a RANK-L inhibitor, is reduced Adhesion also causes myeloma cells to secrete vascular endothelial growth factor leading to new vessel formation, which may encourage tumour growth Alkaline phosphatase levels are normal, reflecting normal or reduced osteoblast activity	Bone pain, especially back Osteoporosis and pathological fractures, especially vertebral Hypercalcaemia symptoms
Renal impairment	Up to 50% of patients	Dehydration (unwell, pain, hypercalcaemia) Hypercalcaemia Hyperuricaemia (increased tumour cell turnover) Sepsis Direct proximal tubule damage from BJP Amyloid deposition	
Anaemia	Commonly present (70% of patients)	Bone marrow infiltration Anaemia of chronic disease Cytokines such as IL-1 impair red cell production, iron incorporation and metabolism	Fatigue
Hypercalcaemia	Around 15% of patients	Widespread bone destruction, as cytokine expression by myeloma cells results in osteoclastic bone resorption	Bone pain Renal impairment
Infection	Common	Myeloma impairs B-cell immunity with suppression of other normal immunoglobulins ('immune paresis') and also suppresses T cells A large quantity of immunoglobulin is around but is monoclonal and usually non-functional and suppresses residual normal polyclonal B cells	Lower respiratory tract infections common
Amyloidosis	10% of myeloma		Primary amyloidosis Kidney usually affected (nephrotic syndrome) Heart failure Peripheral neuropathy
Constitutional symptoms	Common	Cytokines produced by myeloma cells, e.g. TNF-α	Fatigue Weight loss
Hyperviscosity symptoms	More common with hyper-IgM disease (Waldenström's macroglobulinaemia)	IgM load	Headache Blurred vision Dilated retinal veins and haemorrhages
Neurological	Less common		Paraesthesia Spinal cord compression
Other	Uncommon		Bleeding Hepatomegaly Splenomeglay Lymphadenopathy
Asymptomatic	Common		Patients are increasingly diagnosed by way of raised inflammatory markers (plasma viscosity, ESR)

BJP, Bence Jones protein; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; IL, interleukin; RANK-L, receptor activator of nuclear factor-κB ligand; TNF-α, tumour necrosis factor-α.

SUMMARY BOX – ASSESSMENT AND PLAN

There are three highly plausible explanations for his symptoms and investigation results:

◆ *Myeloma with secondary renal failure*, although the normal haemoglobin and skeletal survey are a little unusual with this degree of renal failure. This would not explain the diarrhoea, and, although myeloma is immunosuppressive, infective gastroenteritis of this duration seems unlikely (*Giardia* can be notoriously recurrent and indolent with watery diarrhoea, but is not a typical infectious complication of myeloma).

◆ *Amyloid* causing the raised paraprotein level, renal failure and gastrointestinal involvement. This would be a unifying diagnosis.

◆ *Monoclonal gammopathy of undetermined significance* (MGUS) and a separate cause for the diarrhoea. The hypokalaemia might simply be secondary to chronic diarrhoea but is rather low, especially considering that he has renal failure. A potassium-secreting bowel tumour should certainly be considered. Renal failure is similarly not explained by MGUS (which by definition does not cause organ damage), but this could simply be pre-renal impairment consequent upon dehydration. An ex-heavy smoker, he may also have a precarious cardio-renal balance with incipient heart failure from ischaemia; furthermore, renovascular disease from previous hypertension and smoking may have taken their toll on his renal reserve, with a lower threshold for damage by dehydration. The angiotensin-converting enzyme inhibitor would have been contributory.

Important next steps include:

◆ Referral to a haematologist and bone marrow examination

◆ Sigmoidoscopy and biopsy with Congo red stain for amyloid

◆ Colonoscopy

◆ A renal opinion.

What is the spectrum of plasma cell dyscrasias?

There is a range of plasma cell disorders (Box 2.90).

Box 2.90 **Plasma cell disorders**

- (Multiple) myeloma
- Monoclonal gammopathy of uncertain significance
- Plasmacytoma
- Plasma cell leukaemia
- Non-secretory myeloma
- POEMS syndrome (osteosclerotic myeloma with peripheral neuropathy, organomegaly, endocrinopathies and skin manifestations)
- Amyloidosis
- Hyperimmunoglobulin M (Waldenström's macroglobulinaemia) – a lymphoplasmacytic disorder, with hyperviscosity, perhaps better classified with non-Hodgkin's lymphoma
- Heavy-chain disorders

How common is myeloma?

The UK incidence is around 60 per million (around 3000 new cases per year), and it constitutes 10% of haematological malignancies and 1% of all malignancies. The incidence increases with age, median age of presentation 60–65, peaking at 65–85. Less than 2% are under 40 years of age. It is more common in males, and Afro-Caribbean people.

What causes myeloma?

This is unknown, but there are associations with ionising radiation, occupation (railroad workers and agriculture), rheumatoid arthritis and viruses such as human immunodeficiency virus and human herpes virus 8, together with familial clustering.

How is myeloma diagnosed?

The Duric and Salmon criteria published in 1975 have been widely used. These comprise three major criteria (plasmacytoma on biopsy, bone marrow plasma cells > 30%, monoclonal band – IgG > 35 g/l, IgA > 20 g/l, BJP > 1 g/24 hours) and four minor criteria (bone marrow plasma cells 10–30%, paraprotein present but less than above, lytic bone lesions, low immunoglobulins – immune paresis); diagnosis requires one major criterion plus one minor criterion, two major criteria or three minor criteria. New diagnostic criteria for myeloma by the *International Myeloma Working Group* endorsed in British Haematology Society guidelines are now standard (Table 2.89).

Blood tests

There should be an index of suspicion. Test results warranting consideration of myeloma include unexplained anaemia with rouleaux on the blood film, raised inflammatory markers, renal impairment and hypercalcaemia. When myeloma is suspected, baseline screening investigations should include:

- A full blood count to detect cytopenias resulting from marrow infiltration
- Inspection of the peripheral blood film to look for rouleaux, which may suggest paraproteinaemia
- Serum biochemistry to detect the presence of renal impairment, hypercalcaemia and raised uric acid, and liver function for the total protein concentration (occasionally an unexpectedly raised total protein concentration may be the first clue).

A markedly raised erythrocyte sedimentation rate (ESR) may also suggest myeloma. The C-reactive protein concentration can be mildly raised in patients with myeloma, but typically is not as useful as the ESR as a screening test.

To confirm the presence of a monoclonal paraprotein, serum (and urine) protein electrophoresis is used and can quantify the amount of detectable paraprotein. Testing of serum or urine for free light chains is also important. Immunofixation is used to confirm the monoclonal nature of the protein and characterise the specific immunoglobulin subclass; other plasma cell disorders (such as plasmacytomas) and lymphoproliferative disorders (such as

Table 2.89 Diagnostic criteria for myeloma and monoclonal gammopathy of uncertain significance (MGUS)

	MGUS (common; 1% per year progress to myeloma)	Asymptomatic or 'smouldering' myeloma (12–32% per year progress to symptomatic myeloma)	Symptomatic myeloma
Monoclonal paraprotein (M protein) in serum (or urine)	< 30 g / l	> 30 g / l	> 30 g / l
Bone marrow plasma cell percentage	< 10%	> 10%	> 10%, commonly > 30%
Organ or tissue involvement	No	No	CRAB features of hyper**C**alcaemia from bone destruction, **R**enal impairment, **A**naemia, and lytic **B**one lesions on imaging anaemia Renal disease Bone lesions Other

chronic lymphocytic leukaemia and non-Hodgkin's lymphoma) can also be associated with an M protein. In 97% of patients with myeloma, the combination of serum and urine electrophoresis and immunofixation can detect a monoclonal paraprotein (M protein).

Bone marrow examination

Diagnostic confirmation is by bone marrow examination, traditionally aspiration but increasingly with biopsy and staining for CD138 antibody to detect plasma cells. Plasma cells in myeloma may be morphologically different as well as abundant.

Radiology

A skeletal survey to demonstrate lytic lesions including the classic 'pepperpot skull' has low sensitivity and is less frequently performed. Computed tomography improves sensitivity but is not routine. Magnetic resonance imaging is good for detecting soft-tissue masses, spinal cord compression and the pattern of bone marrow involvement, which has as yet postulated prognostic implications. Positron emission tomography scanning may be used in the future.

What treatments are there for myeloma?

Myeloma is incurable except by bone marrow transplantation although even then cure rates are very small. Median survival is 3–4 years. Treatment of myeloma is currently indicated for symptomatic disease or for myeloma-related organ and tissue impairment. Patients with smouldering myeloma are generally monitored closely as there has been no evidence that early treatment confers a better long-term outcome, although with new therapeutic agents with more favourable toxicity profiles this may change. Patients with myeloma are broadly divided into two treatment groups, depending upon eligiblity for haematopoietic stem cell transplantation (usually autologous).

Patients not eligible for autologous stem cell transplantation

Patients are typically treated with combination chemotherapy until resolution of organ damage and absence of detectable paraprotein. Initial treatment achieves a response (decreased symptoms and tumour burden) in around two-thirds of patients, but the paraprotein is seldom completely dispelled and tends to plateau at a low level after a few months of treatment. Melphalan is very effective, usually given in combination with prednisolone for a few days each month, and more recently with thalidomide. Thalidomide achieves a response in up to 30% of patients with refractory disease, and improves survival in combination with melphalan and response rates in combination with prednisolone but with increased thromboembolic risk. An alternative chemotherapy regimen is cyclophosphamide, dexamethasone and thalidomide. Thalidomide analogues have also been developed (e.g. lenalidomide). Interferon-α as maintenance treatment can prolong the plateau by a few months but has no significant survival effect and frequent side effects. When paraprotein levels start to rise again, indicating relapse, further treatment, often with a different drug or combination, may achieve a further response although remission is usually sustained for a shorter time and ultimately the disease becomes refractory. Bortezomib, a protease inhibitor, is increasingly used.

Patients eligible for autologous stem cell transplantation

Patients often receive repeated cycles of induction chemotherapy to reduce disease bulk (though not excessive as alkylating agents are toxic to stem cells) – usually in combination with thalidomide, lenalidomide, or bortezomib – before stem cell mobilisation and autologous transplantation. Then intensive chemotherapy with autologous stem cell support prolongs remission and survival, although it does not cure. Allogeneic transplantation, suitable for patients up to 55 years of age with a matched sibling donor, is potentially curative. It carries high transplant mortality but lower relapse rates because of graft versus myeloma effect. Reduced intensity conditioning regimens may extend the use of allogeneic transplantation to older patients.

Other treatments

All patients require bisphosphonates, which reduce pathological fractures and skeletal related events, and zoledronic acid may be the bisphosphonate of choice.

Adjuvant treatments in the form of localised radiotherapy may also be used for patients with symptomatic lytic lesions.

Patients with recurrent infections resulting from secondary hypogammaglobulinaemia may benefit from regular intravenous immunoglobulin replacement.

What prognostic factors are there in myeloma?

A prognosis staging system is outlined in Table 2.90, as are other prognostic factors in symptomatic myeloma.

Untreated myeloma can lead to debilitating complications such as pathological fractures from lytic lesions, irreversible renal failure, or rarely spinal cord compression from extramedullary plasmacytomas. Delays in diagnosis are associated with a higher rate of complications and reduced disease-free survival.

How would you manage suspected monoclonal gammopathy of uncertain significance (MGUS)?

MGUS is common, and 10% of older people have a small detectable paraprotein. If anaemia, renal impairment, hypercalcaemia and evidence of organ involvement are excluded people can be observed. The combination of anaemia and a raised ESR or plasma viscosity should always prompt a paraprotein search. Referral to a haematologist is indicated if there is a high paraprotein, immune paresis or evidence of organ or tissue effects.

Table 2.90 Prognosis in myeloma

Stage	Features
I	Serum β_2-microglobulin < 3.5 mg / l (and albumin > 35 g / l)
II	Neither I nor III
III	Serum β_2-microglobulin > 5.5 mg / l
Other prognostic factors	
Raised C-reactive protein	
Atypical plasma cells	
Cytogenetic abnormalities, e.g. trisomy 3, 7, 9, 11 or loss of 13q–	

What is a plasmacytoma?

This is a localised cluster of myeloma cells that may produce any of the usual symptoms or pressure effects such as spinal cord compression (may also occur from vertebral collapse).

What is amyloidosis?

Amyloidosis refers to the infiltration of various organs with insoluble eosinophilic protein fibrils composed of amino-acid chains arranged in a cross-beta pattern together with other components such as serum amyloid P. Amyloidosis is now classified according to the fibrillary protein.

Classification

- In *AL amyloidosis* the protein is an immunoglobulin light chain or fragment produced by a clone of plasma cells, although in most AL amyloidosis the plasma cell burden is typically low and only about 10% of AL amyloidosis is due to myeloma. Heavy chain amyloidosis is described.
- Reactive amyloidosis (*AA amyloidosis*), formerly termed secondary amyloidosis, is the most common systemic amyloidosis. It is associated with chronic inflammation and occurs in various inflammatory, infective and neoplastic disorders. The precursor amyloidogenic protein is a normal-sequence apo-SAA (serum amyloid A protein), which is an acute-phase reactant.
- Those formerly classified as 'senile' amyloid and many with familial amyloidosis are associated with fibrils of transport protein transthyretin (TTR) and are now termed ATTR.

In all forms of amyloidosis the cell secretes the precursor protein in a soluble form that becomes insoluble at a tissue site, compromising organ function. Many patients with AL, AA or ATTR amyloidosis have multi-system involvement. Some conditions, however, are due to localised amyloid fibril production; these include Alzheimer's disease (β-protein precursor), Creutzfeldt–Jakob disease (prion protein), hereditary cerebral haemorrhage with amyloidosis, various forms of ocular amyloidosis , pituitary amyloidosis (prolactin), cutaneous amyloidosis (keratin), medually thyroid cancer (calcitonin) and isolated aortic and atrial amyloidoses.

Clinical features

The kidney is the most common site of damage in AL and AA amyloidosis, usually manifested as nephrotic syndrome often with massive proteinuria and oedema resistant to diuretics. Renal failure is inevitable unless amyloid formation can be halted and is rare without marked proteinuria unless the amyloid is predominantly confined to the tubulo-interstitium and blood vessels, sparing glomeruli. Amyloidosis (with the exeption of AA amyloidosis) also causes concentric left ventricular hypertrophy, and a restrictive cardiomyopathy results from restriction to dilation and filling that reduces cardiac output despite a

Table 2.91 Clinical features of amyloidosis

Kidney	Nephrotic syndrome Renal failure (an unusual combination which should always prompt consideration of amyloidosis)
Heart	Restrictive cardiomyopathy Cardiac arrhythmias Valvular heart disease Coronary disease
Gut and liver	Ischaemic colitis Hepatosplenomegaly and altered liver enzymes
Lung	Parenchymal infiltration Pleural effusions
Nervous system	Autonomic neuropathy Peripheral neuropathy
Other	Macroglossia (specific to AL amyloidosis, occurring in around 20%)

relatively preserved ejection fraction. Clinical features of amyloidosis are given in Table 2.91.

Diagnosis

Initial investigation is aimed at confirming amyloidosis by tissue biopsy. Biopsy of an affected organ is usually diagnostic, although fat aspiration or rectal biopsy may be considered. Amyloid fibrils classically produce red–green birefringence under polarised light when stained with Congo red.

Once amyloidosis is confirmed, the amyloid type is established. Antibodies have been developed for most known amyloid proteins. In situations where immunohistochemistry is inconclusive, DNA analysis or fibril protein sequencing can be used. In AL amyloidosis it is important to look for evidence of an underlying plasma cell dyscrasia such as myeloma.

As well as the type of amyloidosis, it is imperative to establish the extent of organ involvement. Serum amyloid P (SAP) scintigraphy is routinely performed in most individuals referred for assessment but is unable to image amyloid in the moving heart, and echocardiograms are essential. Nerve conduction studies may be required where neuropathy is the predominant symptom, and nerve biopsy is occasionally required to establish the diagnosis.

Poor prognostic factors at presentation are echocardiographic evidence of cardiac involvement (left ventricular hypertrophy in the absence of hypertension is very suggestive, as are right ventircular thickening without pulmonary pathology, and thickening of valves and the interatrial septum), a large amyloid load on SAP scintigraphy, autonomic neuropathy, hyperbilirubinaemia and associated myeloma.

Treatment

This depends upon the type of amyloidosis. AL amyloidosis may be considered for chemotherapy, including high-dose chemotherapy with peripheral autologous stem cell rescue. AA amyloidosis often responds to reduction of the SAA load with treatment of the underlying inflammatory condition, increasingly with cytokine-modulating therapies that suppress the acute-phase response such as tumour necrosis factor and interleukin-1 inhibitors. Specific organ treatments such as treating heart failure are also needed.

Other problems in acute and general medicine and elderly care

CASE 2.39 HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mr Jason Moriarty, aged 35 years

Thank you for admitting this gentleman with human immunodeficiency virus who has become breathless over a few days. He is slightly tachypnoeic, his temperature is 38°C, and he looks sweaty and unwell. I am concerned about pneumonia.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Jason Moriarty is a 35-year-old man who is human immunodeficiency virus (HIV)-positive, the infection acquired 12 years ago through homosexual intercourse. He has taken highly active antiretroviral treatment (HAART) for the past few years, although concordance with treatment has recently been problematic because of life stresses and side effects of treatment, and he has missed a number of follow-up appointments with his specialist. His last documented CD4 count was 250/μl,

Box 2.91 ***Pneumocystis jirovecii* pneumonia**

Formerly known as *Pneumocystis carinii* pneumonia (PCP), this is a fungal infection that remains a common acquired immunodeficiency syndrome (AIDS)-defining disease and the most common life-threatening infection in AIDS. Most patients develop the disease without highly active antiretroviral treatment (HAART). It is common in patients who cannot tolerate or who are non-compliant with HAART and probably arises as new infection, rather than reactivation as was once thought.

It causes a non-productive cough and breathlessness over 2–3 weeks, often with severe hypoxia, and minimal chest signs.

measured around 4 months ago. He now presents with a short respiratory illness comprising a dry cough, breathlessness and fever. He is worried about the possibility of *Pneumocystis jirovecii* pneumonia. His past medical history other than HIV is uneventful. In terms of HIV he has had problems with recurrent herpes zoster, recurrent candidiasis and white oral plaques. He has recently separated from his long-term partner and lives alone and describes himself as very depressed. He has given up work as a store designer. He is not infected with the hepatitis C virus.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Consider HIV-associated respiratory disease (but also the usual causes of breathlessness).** HIV-associated respiratory disease is common, affecting more than 50% of patients. Typical respiratory infections that affect non-HIV-infected people are common in early disease, but may be more severe. These include upper respiratory tract infections, sinusitis, bronchitis and bacterial pneumonia. With CD4 counts under 200/μl, *P. jirovecii* is a problem (Box 2.91). Tuberculosis can occur at any stage. Non-infectious respiratory diseases in HIV include Kaposi's sarcoma, lymphoma, lung cancer and non-specific interstitial pneumonitis, the last of these being possible when the CD4 count is normal.

Patient perspective

Explore his reasons for stopping treatment, not least his depression.

Past medical history

Explore the duration of his diagnosis, how it came to be diagnosed and the likely mode of transmission and explore his list of symptoms and opportunistic infections to date and what treatments he has received for these.

Drug and allergy history

He has been taking HAART, but his poor concordance recently will have exposed him to a high risk of vigorous mutation of HIV with a further fall in the CD4 count and opportunistic infections, notably *P. jirovecii*. Enquire about side effects of HAART that might have contributed to his stopping treatment, rather than assuming it was exclusively depression.

Family history

Relevance here is unlikely.

Social history

Explore what risk modification behaviour he has used to reduce the risk of transmission.

SUMMARY BOX – ASSESSMENT AND PLAN

- He should have all the usual investigations first – a full screen of haematobiochemisty, a chest X-ray and arterial blood gases. The chest X-ray appearances in *Pneumocystis jirovecii* pneumonia (formerly known as PCP) range from mild, bilateral, perihilar interstitial infiltrates to confluent, diffuse alveolar opacification, which can progress over a few days. Other appearances are possible, including upper zone infiltrates, pulmonary nodules or lobar consolidation.
- While the differential diagnosis in patients not known to be infected with human immunodeficiency virus (HIV) includes atypical pneumonia, a careful history in HIV usually reveals other signs of immune compromise such as oral candidiasis. Lymphopenia is common. *P. jirovecii* pneumonia may be confirmed by Giemsa staining or polymerase chain reaction of induced sputum or bronchoalveolar lavage fluid.
- Treatment is usually started empirically in patients with a presumptive diagnosis of *P. jirovecii* pneumonia and a CD4 count below 200/μl. First line is co-trimoxazole (trimethoprim-sulfamethoxazole), initially intravenously except in mild disease without hypoxia. Alternatives include clindamycin with primaquine, dapsone with trimethoprim or atovaquone. Pentamidine is now seldom used. Corticosteroids are given for moderate to severe disease.
- Prophylaxis uses co-trimoxazole first line. Primary prophylaxis is indicated for a CD4 count below 200/μl, HIV-associated constitutional features or a history of any acquired immunodeficiency syndrome defining diagnosis. Secondary prophylaxis is indicated for all patients. Prophylaxis may be discontinued if patients on highly active antiretroviral treatment exhibit sustained increases in CD4 counts greater than 200/μl and suppression of viral load below the limits of detection.

Discussion

What do you know about the epidemiology of HIV infection?

HIV affects 40 million adults worldwide. The major route of transmission is heterosexual (> 75%). About 5–10% of new infections are in children, usually acquired during pregnancy, birth or breastfeeding. Injecting drug users represent a smaller proportion. Increasingly, as an effect of longer term survival, HIV is seen as a chronic disease and in older people.

What types of HIV are there?

HIV-1 has multiple groups and genetic subtypes, and mutation of strains is part of its ability to survive. HIV-1 is derived from the simian immunodeficiency virus of chimpanzees. HIV-2 is quite dissimilar, common in parts of Africa and genetically closer to the sooty mangabey virus and inherently resistant to non-nucleoside reverse transcriptase inhibitors. Related viruses causing immunodeficiency infect other animals including cats, sheep, goats and horses.

Describe the structure of the HIV virion

HIV is a retrovirus comprising two RNA copies of the genes *env*, *gag* and *pol*; *env* encodes glycoprotein gp160, which is cleaved to form the gp120 surface molecule and the gp41 transmembrane molecule; *gag* encodes the precursor to the capsid molecules p24, p17, p9 and p6, the latter enabling budding of the virus; *pol* encodes the enzymes reverse transcriptase, protease and integrase. There are also regulatory genes – *tat*, which regulates transcription, *rev*, which aids translation, and *nef*, which recruits lymphocytes to infected macrophages to aid spread.

How does the virus replicate?

gp120 binds to CD4 surface antigens on T lymphocytes and macrophages. Entry of the HIV virion into host cells also requires the interaction of gp120 with chemokine co-receptor CCR5, found predominantly on macrophages, and with chemokine co-receptor CXCR4, found predominantly on lymphocytes. Binding leads to a conformational change in the envelope molecule such that a hydrophobic sharp tip of the transmembrane protein gp41 is exposed, which can penetrate the host cell (Fig. 2.12-1). Viral capsid is then released into the cytoplasm of the host cell. Reverse transcriptase converts the RNA genome into double-stranded DNA. DNA is then integrated into the host genome under the control of viral integrase. The integrated gene is treated by the host as a normal gene, transcribed and translated into a new virion aided by the regulatory genes, before budding out of the cell. Replication is rapid, with perhaps 10^{10} viruses produced daily and 10^8 host cells destroyed, especially at lymph node sites.

What is the pathogenesis of HIV infection and why do some people appear to be 'immune' to HIV?

Entry of HIV into the body

The virus transmitted sexually across mucous membranes is almost exclusively macrophage tropic, and on infecting macrophages is transported to draining lymph nodes. People homozygous for CCR5 mutations appear to be protected from acquiring HIV by this route, and heterozygotes progress slowly. Macrophage-tropic HIV can infect central nervous system microganglia and probably accounts for HIV brain disease. Lymphocyte-tropic HIV may be acquired directly from contaminated blood but in most patients appears later in the course of infection as the macrophage-tropic virus evolves to harness the CXCR4 receptor.

Early immune responses

Innate immune responses are activated immediately but cannot stop the virus. Acquired, adaptive immune responses involve clonal expansion of B cells to produce antibodies and T-cell responses. Acute infection with HIV leads to rapid replication and within weeks several million copies of the HIV genome are found in plasma, the peak level determined by host immunity. However, this number rapidly declines to a steady state, because initial numbers comprise a wide variety of genetically different viruses because reverse transcriptase allows significant mutations as an in-built survival mechanism. Ultimately, the mutation potential of HIV is an important factor in the failure of host immunity to contain it, and why a cure remains elusive.

Antibody responses

Antibodies against *gag* p24 and p17 tend to appear first within a few weeks, but are non-neutralising and non-sustained. Antibodies against envelope proteins needed for cell entry appear later – against a V3 loop variable region of gp120, transmembrane protein gp41 and binding sites for CD4 and chemokine co-receptors CCR5 and CXCR4. However, these later antibodies tend to be directed against less crucial sites of these envelope proteins and, even when neutralisation occurs, HIV can simply mutate.

Cellular responses

CD8 (cytotoxic) lymphocytes interact via their T-cell receptor (TCR) with MHC or human leucocyte antigen (HLA) class I molecules of infected cells presenting HIV peptides (Fig. 2.12-2). CD8 cells lyse infected cells directly and produce cytokines such as interferon-γ and tumour necrosis factor-α and chemokines such as macrophage inflammatory proteins 1α and 1β and RANTES (regulated on activation normal T-cell expressed and secreted) that suppress replication or block entry of HIV into CD4 cells. CD4 (T-helper) lymphocytes interact via their TCR with the MHC class II molecules of specialised antigen-presenting cells (APCs) presenting shed protein particles of the HIV virus (Fig. 2.12-3). CD4 cells produce cytokines that perpetuate the T-helper response and collaborate with B cells in the production of specific antibodies (Case 2.46).

The importance of long-term non-progressors (LTNPs) in understanding HIV pathogenesis and research into treatments and vaccines

HIV induces chronic immune hyperactivity that causes the development of acquired immunodeficiency syndrome (AIDS). This process occurs readily in some individuals but is absent in others. A small proportion of HIV-infected individuals remain symptom free and with low viral loads and stable CD4 counts for up to 20 years, and are known as LTNPs. Many have strong neutralising antibody responses. Many have mutant chemokine co-receptors. Thus, host immune genetics are vital in

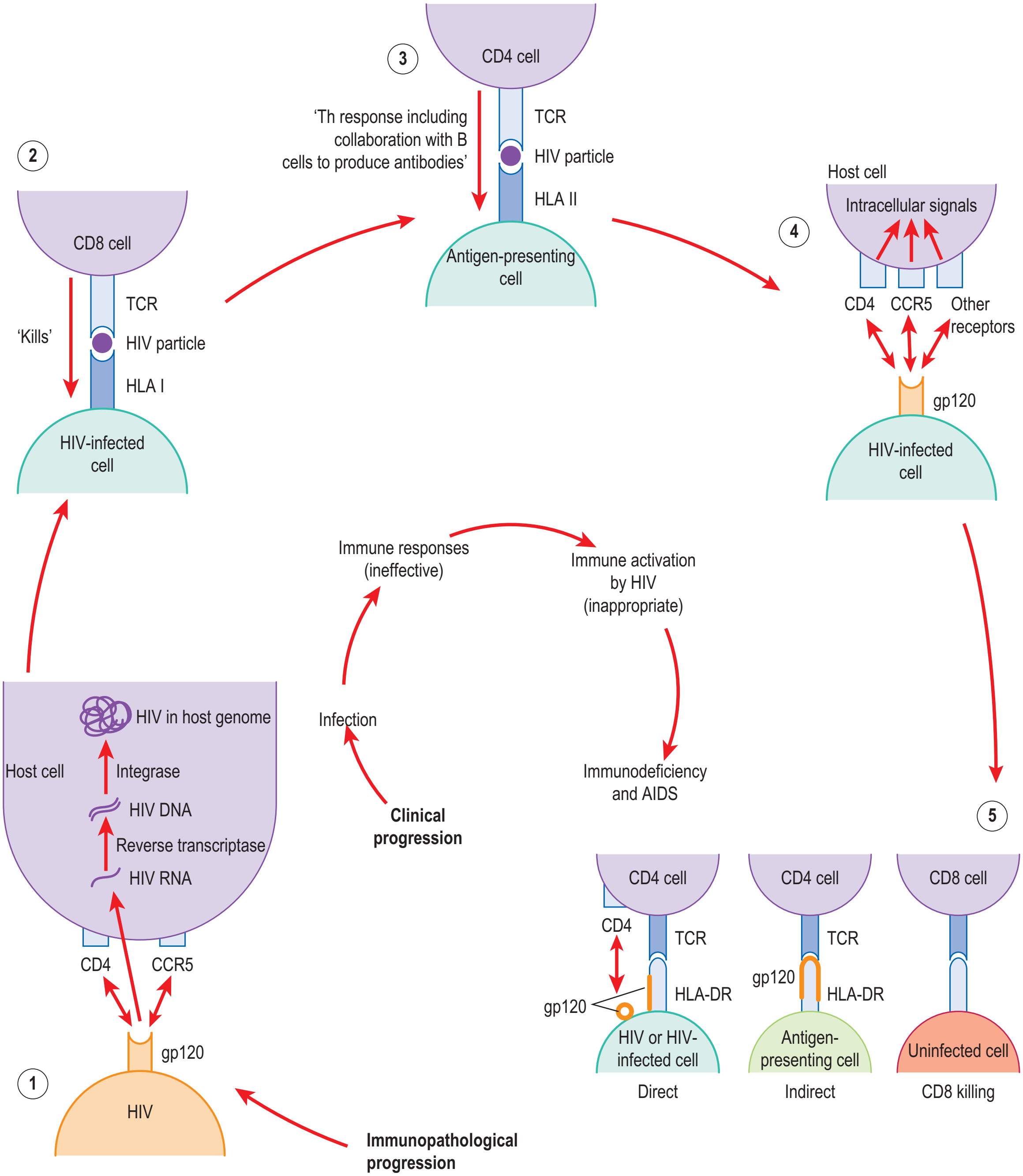

3
CD4 cell
'Th response including collaboration with B cells to produce antibodies'
TCR
HIV particle
HLA II
Antigen-presenting cell
2
CD8 cell
'Kills'
TCR
HIV particle
HLA I
HIV-infected cell
Host cell
Intracellular signals
4
CD4
CCR5
Other receptors
gp120
HIV-infected cell
Immune responses (ineffective)
Immune activation by HIV (inappropriate)
Infection
Immunodeficiency and AIDS
Clinical progression
HIV in host genome
Host cell
Integrase
HIV DNA
Reverse transcriptase
HIV RNA
CD4
CCR5
gp120
1
HIV
Immunopathological progression
5
CD4 cell
CD4
TCR
HLA-DR
gp120
HIV or HIV-infected cell
Direct
CD4 cell
TCR
gp120
HLA-DR
Antigen-presenting cell
Indirect
CD8 cell
Uninfected cell
CD8 killing

Figure 2.12 Human immunodeficiency virus (HIV). 1. HIV entry into host cell. 2. CD8 response to HIV. 3. CD4 response to HIV. 4. Immune activation by HIV. 5. Alloactivation and CD8 killing of host cells. AIDS, acquired immunodeficiency syndrome; gp, glycoprotein; HLA, human leucocyte antigen; TCR, T-cell receptor.

development of AIDS. Chimpanzees and human LTNPs appear to be resistant to the inappropriate immune activation that characterises HIV infection and progression to AIDS. This suggests potential for the immune system to be manipulated in susceptible individuals to induce a LTNP status.

HIV – the paradox of evading host immune responses yet provoking immune activation

Evading host immunity

HIV employs many mechanisms to evade immune responses. These include: antigenic variability, latent infection of CD4 cells such that these are not visible for CD8 cytotoxicity; masking of target structures, e.g. non-immunogenic proteins coat more crucial envelope proteins and protect these from antibody neutralisation; putting host proteins into the virion itself to protect itself from complement; downregulation of HLA in infected cells; mutation. Minimal HIV mutations are enough to prevent HLA binding of HIV particles for antigen presentation, for HIV particles to evade TCR recognition or for HIV to evade antibody responses; the V3 loop of the envelope protein gp120 exhibits many mutations whilst antibodies to the V3 loop tend to be specific to a particular strain, and whilst the CD4-binding domain of gp120 is highly conserved between strains, antibodies to it tend to exhibit poor neutralising ability.

Immune activation

The paradox is that HIV evades host immune responses, and yet provokes the exact opposite, inappropriately activating many parts of the immune system such as APCs, HIV-specific T lymphocytes, other T lymphocytes, B lymphocytes, and natural killer cells.

How HIV triggers immune activation is unclear. HIV destroys a large number of CD4-CCR5 memory T lymphocytes in the intestinal mucosa during acute infection, and it might be at this time that the immune system becomes chronically activated, although against this theory is that measles and other viruses also cause massive T-lymphocyte losses and transient immunodeficiency without provoking an AIDS-like syndrome. Other theories support the longer term influence of the virus and its gene products in promoting chronic immune stimulation. The envelope glycoprotein gp120 is most implicated in the pathogenesis of immune activation since it interacts with CD4 and chemokine co-receptors such as CCR5. Chemokine receptor interactions may influence activation, signals induced as a result of any interactions may trigger activation, and susceptibility to an additional inappropriate stimulus may be the difference between progressors and LTNPs (Fig. 2.12-4).

Autoimmune responses resulting from molecular mimicry may contribute to immune activation and AIDS pathogenesis. Partial sequence mimicry can be sufficient to induce this. There is, for example, structural mimicry between a region of the V3 loop of gp120 and a binding region of certain chemokines, allowing either to potentially interact with chemokine co-receptors; however, any response would probably only selectively activate a few autoreactive T lymphocytes against the select host protein and not provoke widespread immune activation. A more compelling theory for molecular mimicry in HIV's pathogenesis involves HLA repertoires, which almost certainly underlie the differing responses between progressors and LTNPs. Some HLA types afford greater protection against HIV. This may be because some HLA types are more likely to present antigenic peptides of HIV more suitable for long-term viral suppression or it may be because some HLA types are more likely to select a T-cell repertoire more responsive to HIV. However, a region of HIV's envelope protein gp120 known as C5 is homologous with a region of host HLA-DR (class II), such that both appear capable of binding to CD4. CD4 cells may respond to gp120-C5 by a variety of possible mechanisms. HIV or HIV-infected cells may directly stimulate CD4 with gp120-C5 or by engaging the TCRs of a CD4 cells with gp120-C5 complexed with HLA-DR; APCs may indirectly stimulate CD4 (or CD8) cells by engaging the TCR of CD4 cells with gp120-C5 presented by HLA-DR (Fig. 2.12-5). It may then be that the TCRs of both infected and uninfected T lymphocytes and other host cells become capable of being activated not just by HIV but by host HLA-DR, the latter known as auto- or alloactivation (HLA-DR acting as an alloantigen), similar to the phenomenon seen in graft versus host disease. There may then be CD8 cytotoxic responses against uninfected native HLA-DR cells normally presented as part of the host self-repertoire (Fig. 2.12-5). Antibodies against the gp120-C5 region strongly correlate with slower HIV disease progression, raising the question of a non-neutralising antibody targeting the gp120-C5 domain being used as a vaccine.

Immune deficiency

Immune deficiency in HIV and AIDS has traditionally been attributed to direct infection and loss of cells by HIV, notably CD4 cells.

However, immune activation is associated with anergy and apoptosis involving uninfected cells, and loss of antigen-specific responses, long before CD4 T lymphocyte counts decline. And so it appears that immune activation is key to AIDS pathogenesis, contributing significantly to cell loss and immune deficiency. The problem is that it is the immune system itself that is attacked by this immune activity, and so HIV might be considered the ultimate autoimmune disease in which HIV 'tricks' the immune system into destroying itself rather than the virus. Consequently, immune activation markers may have greater prognostic significance than viral load or CD4 counts, high viral loads leading to disease only if accompanied by inappropriate immune stimulation, but the latter leading to disease even with low viral loads. Further, the reduced pathogenesis of HIV-2 appears to reflect lower immune activation, also the case with LTNPs who either lack appropriate receptors to engage in inappropriate immune responses or can neutralise triggers to such responses.

Why are the symptoms of opportunistic disease in HIV often atypical?

The eloquent workings of the immune system are illustrated best when at fault. HIV, which parasitises the immune system, affirms that it is ravaged defence rather than microbiological attack that causes the clinical manifestations of HIV disease and AIDS. Just as it is the powerful pro-inflammatory response causing fever, pharyngitis and pain in a common cold and not the furtive adenovirus, so impoverished inflammatory potential limits symptoms. Whilst meningococcal meningitis in immunocompetent individuals rapidly results in severe headache with a life-threatening acute-phase response, cryptococcal meningitis in HIV-infected individuals may be insidious with minimal signs despite a cerebrospinal fluid overrun with organisms.

What is the natural history of HIV infection?

The stages of HIV infection are illustrated in Table 2.92.

Other than *P. jirovecii*, what other fungal infections can cause lung disease in HIV?

Cryptococcus neoforms, *Histoplasma capsulatum* and *Coccidioides immitis* are uncommon in the UK but occur in Africa and the USA. Treatment is with fluconazole or amphotericin.

What do you know about mycobacterial infection in HIV?

Tuberculosis may occur at any stage in HIV infection. There is a higher risk of tuberculosis latent reactivation, new acquisition, developing primary progressive disease or miliary, extrapulmonary or disseminated disease. More than two-thirds with tuberculosis present with pulmonary tuberculosis.

In early disease with near normal CD4 counts its behaviour is similar to that in non-HIV-infected adults with post-primary disease, i.e. cough, haemoptysis, dyspnoea, fever, night sweats or weight loss. The chest X-ray may show upper zone opacification, the tuberculin test is positive and expectorated sputum or bronchoalveolar fluid analysis is often smear positive.

More advanced HIV can cause atypical tuberculosis presentation, often with weight loss or fever that may be mistaken for HIV 'constitutional' disease. The chest X-ray may resemble primary tuberculosis with hilar lymphadenopathy, diffuse shadowing or even pleural effusion, or may be normal, the tuberculin test is usually negative and sputum or bronchoalveolar fluid analysis is often smear negative but culture positive.

Extrapulmonary tuberculosis is common with CD4 counts under 150/μl and often affects the lymph nodes, bone marrow, liver or pericardium.

Treatment for tuberculosis in HIV uses the standard four-drug regimens for 6 months used in non-HIV-infected individuals, but side effects are higher and HAART should be started.

Multidrug resistant tuberculosis is common, often as a result of poor concordance with therapy.

Prophylaxis against tuberculosis in HIV-infected individuals is without consensus.

Tuberculosis is a potent stimulator of cell-mediated immunity and there have long been concerns that it may accelerate HIV replication in infected cells; this is also a concern with some other HIV opportunistic infections such as syphilis.

Other mycobacterial diseases occur in HIV. Disseminated *Mycobacterium avium intracellulare* causes fevers, weight loss and anaemia, and may cause diarrhoea. It is a late manifestation of HIV with CD4 counts less than 50/μl. Treatment is with azalide antibiotics such as azithromycin.

What HIV-related oral diseases do you know of?

Oral candidiasis and oral herpes simplex are common. Oral hairy leucoplakia refers to asymptomatic white corrugations on the side of the tongue and is the result of Epstein–Barr virus infection; it is highly suggestive of HIV infection, whereas oral candidiasis is common in many hospitalised and unwell patients.

What HIV-related oesophageal diseases do you know of?

Oesophageal candidiasis is the most common cause of oesophageal symptoms in HIV and an AIDS-defining condition, although it does occur not infrequently outside the setting of HIV. It causes pain on swallowing and dysphagia. It usually responds to single-dose fluconazole and, if that fails, itraconazole. Relapses are uncommon after HAART.

Oesophageal ulceration may be the result of cytomegalovirus or herpes simplex virus infections. Cytomegalovirus produces discrete ulcers of the lower oesophagus or haemorrhagic oesophagitis. Treatments include ganciclovir or foscarnet, and relapses are uncommon after HAART. Herpes simplex virus produces discrete, vesicular lesions and is treated with aciclovir.

What HIV-related diarrhoeal diseases do you know of?

Diarrhoea can occur at any stage of HIV disease and may be caused by various pathogens. It occurs in almost all patients at some point and is a presenting feature of AIDS in a considerable proportion.

Bacterial infections are common and include *Salmonella* and *Campylobacter* spp.

Cryptosporidium parvum is a zoonotic intestinal parasite. Cryptosporidiosis causes self-limiting diarrhoea in HIV-negative people and those with CD4 counts > 200/μl. Chronic diarrhoea with weight loss and malabsorption occur in immunodeficiency. It is identified on stool

Table 2.92 Stages of human immunodeficiency virus (HIV) infection

Stage	When it occurs	Clinical manifestations		Management implications
Seroconversion	6–12 weeks CD4 count > 500 / μl	Seroconversion illness lasting 7–10 days in 70–80% with fever, malaise, arthralgia, maculopapular rash, myalgia, mouth ulcers and pharyngitis in decreasing likelihood		Establish diagnosis
		Opportunistic infection if CD4 drops transiently below 200 / μl		
		Neurological problems, e.g. aseptic meningitis, facial palsy, Guillain–Barré syndrome, transverse myelitis		
CDC category A disease	Asymptomatic disease CD4 count usually 350–800 / μl (normal is around 600–1200 cells / μl)	Usually asymptomatic slow decline in CD4 count over 6–8 years		Minor opportunistic infections
		Rapid progression usually implies virus using CXCR4 co-receptor		
		Long-term non-progressors (up to 5–10%)		
		Persistent generalised lymphadenopathy may be the presenting feature of HIV infection; it persists for over 3 months in at least two extrainguinal sites, usually symmetrically		
CDC category B disease	CD4 count 200–350 / μl	Herpes simplex Herpes zoster Pulmonary tuberculosis Streptococcal pneumonia (often recurrent and severe) Recurrent oropharyngeal or vaginal candidiasis (especially as approach 200 / μl) Oral hairy leucoplakia Salmonellosis Kaposi's sarcoma Cervical intraepithelial neoplasia II–III Lymphoid interstitial pneumonitis HIV-associated idiopathic thrombocytopenic purpura	**AIDS-defining conditions** *Pneumocystis jirovecii* pneumonia (formerly PCP) Miliary or extrapulmonary tuberculosis Extrapulmonary histoplasmosis or coccidioidomycosis Disseminated *Mycobacterium avium intracellulare* Oesophageal candidiasis Chronic mucocutaneous herpes simplex Chronic cryptosporidial diarrhoea Recurrent non-typhi *Salmonella* septicaemia HIV-associated dementia Cerebral toxoplasmosis Cryptococcal meningitis Cytomegalovirus retinitis or colitis Progressive multifocal leucoencephalopathy Primary cerebral lymphoma HIV-associated wasting Non-Hodgkin's lymphoma Kaposi's sarcoma Invasive cervical cancer	Start HAART
CDC category C disease	CD4 count < 200 / μl	Kaposi's sarcoma *Pneumocystis jirovecii* pneumonia Cerebral toxoplasmosis Miliary or extrapulmonary tuberculosis Mucocutaneous herpes simplex Oesophageal candidiasis *Cryptosporidium* infection *Microsporidium* infection HIV-associated wasting Peripheral neuropathy		Opportunistic infections and neoplasms much more likely
CDC category D disease	CD4 count < 100 / μl	Disseminated *Mycobacterium avium intracellulare* Cerebral toxoplasmosis Cryptococcal meningitis (occasionally pneumonia or skin lesions) Systemic fungal infection (especially *Cryptococcus neoformans*) Cytomegalovirus retinitis / colitis Primary CNS lymphoma Non-Hodgkin's lymphoma HIV encephalopathy leading to HIV-associated dementia Progressive multifocal leucoencephalopathy		Potentially fatal complications

AIDS, acquired immunodeficiency syndrome;CDC, US Centers for Disease Control and Prevention; CNS, central nervous system; HAART, highly active antiretroviral treatment.

culture. *Microsporidium* causes less severe but similar symptoms. Treatment is with HAART aiming for a CD4 count over 200/µl.

Cytomegalovirus may affect the entire bowel, including the oesophagus, but most commonly causes inflammatory colitis with bloody diarrhoea in highly immunosuppressed patients.

What HIV-related liver diseases do you know of?

These include associated viral hepatitis-related diseases, cholestatic liver disease, malignant liver disease and drug-related hepatitis and cholestasis.

Is kidney disease common with HIV?

Kidney disease is increasingly seen in HIV, although usually not due directly to HIV or HAART, but to the ageing population of patients with HIV and associated vascular disease, or to drugs used to treat HIV complications.

What is HIV-associated wasting?

Loss of body weight by more than 10% without an obvious cause is an AIDS-defining condition but is now uncommon in the developed world. A pathogen should therefore generally be sought.

What is the range of HIV-related neurological disease?

HIV may affect any part of the neuro-axis during evolution from seroconversion to late stage HIV, from direct viral infection, opportunistic infections, HIV-related malignancy or AIDS-defining cancers, antiretroviral drug therapy or other less well-elucidated associations such as vascular events. HAART has altered the epidemiology though not the range of diseases encountered. Neurological disease is a presenting feature in 2–3% of cases (15% pre-HAART). Around two-thirds result from opportunistic infection or HIV-related malignancy, and represent a late stage with profound immunodeficiency (CD4 count < 100/µl). The type and severity of disease depend on the CD4 count and timing of presentation, although age, ethnicity, drug therapy and comorbidities are other influences. The range of HIV-related neurological disease is outlined in Box 2.92.

What is Kaposi's sarcoma?

This is the most common malignancy associated with HIV-1 and is caused by human herpes virus 8. It is probably derived from lymphovascular endothelium. Most patients present with mucocutaneous disease with discrete, non-itchy, non-tender, purple papules that are often arranged symmetrically on the limbs, trunk, face or hard palate. These may turn brown over time. Oedema from lymphatic involvement can precede lesions. Disease may be indolent or rapidly progressive with visceral as well as cutaneous involvement, especially of the lungs or gastrointestinal tract. HAART and local radiotherapy or intralesional chemotherapy are used for cutaneous disease and systemic chemotherapy, with liposomal doxorubicin or paclitaxel, may be needed in systemic disease.

What other AIDS-related cancers do you know of?

As HAART has reduced infectious disease complications and improved survival in HIV, longer term malignant complications have become more prevalent. High-grade B-cell non-Hodgkin's lymphoma is 100 times more common in HIV-infected individuals. Systemic non-Hodgkin's lymphoma accounts for about 30% of malignancy-related death in HIV-positive individuals. HAART has not led to a dramatic decrease in the incidence. Primary central nervous system lymphoma is rare in the general population but was common in HIV before HAART. It is

Box 2.92 **The range of human immunodeficiency virus (HIV)-related neurological disease**

Directly HIV related

Primary infection (seroconversion)

This may be associated with aseptic meningitis, facial palsy, Guillain–Barré syndrome (GBS) or transverse myelitis. Aseptic meningitis is most common, indistinguishable from enteroviral or other lymphocytic meningitides (normal glucose, slightly elevated protein) but may be associated with bilateral facial palsy. GBS is unusual, but increasingly HIV is a cause and should be considered.

HIV-associated neurocognitive disorder (HAND)

More commonly, HIV-related pathology manifests as chronic and slowly progressive disease – HAND, myelopathy, peripheral neuropathy, myopathy – when highly active antiretroviral treatment (HAART) has limited or no effect. HAND is an umbrella term for the wide range of neurodegenerative disease caused by chronic HIV infection including asymptomatic neurocognitive impairment, HIV-associated mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). HAND affects 29–69% of people with HIV and is associated with central nervous system viral load, current and nadir CD4 counts and co-infection with hepatitis C. MND occurs with CD4 counts < 500 and > 200 and HAD, the most severe form of HAND with severe cognitive impairment, and sometimes spasticity and extrapyramidal features, with CD4 counts < 200. HAND affects the central white matter, brainstem and spinal cord. It can be prevented, but not reversed, with HAART. The differential diagnosis is cerebral opportunistic infections.

Vacuolar myelopathy

This is HIV-specific and can occur at any stage but is more likely with CD4 counts < 50. It causes spastic paraparesis, the differential diagnosis being spinal cord opportunistic infection.

Box 2.92 **The range of human immunodeficiency virus (HIV)-related neurological disease—cont'd**

Distal sensory peripheral neuropathy

This is an uncommon but disabling complication associated with severe immunosuppression.

Opportunistic infections

These seldom occur until CD4 counts are < 200.

Cerebral toxoplasmosis

Toxoplasma gondii is a widespread protozoan with feline hosts, primary human infection occurring usually as a result of ingestion of food contaminated with cat faeces or undercooked meat from an infected animal. Development of cell-mediated immunity after acute infection results in control but not eradication. The ensuing chronic or latent phase of infection is characterised by persistence of the organism in tissues, primarily brain, skeletal muscle and heart. A chronically infected individual who develops defects in cell-mediated immunity is at risk of re-activation, primarily as toxoplasmic encephalitis (TE), but the disease often causes focal brain lesions in HIV-infected patients. Characteristically, TE has a subacute onset with focal neurological abnormalities (commonly motor weakness and speech disturbance), frequently accompanied by headache, cognitive disturbance, seizures and fever. HIV-infected patients may also develop extracerebral toxoplasmosis with or without encephalitis, ocular (chorioretinitis) and pulmonary disease (often similar to *Pneumocystis jirovecii*) the most common.

Cerebral toxoplasmosis is diagnosed by demonstration of typical multiple ring-enhancing lesions with marked surrounding oedema – typically in the cortex, brainstem or extrapyramidal system – on magnetic resonance imaging (MRI) in patients with CD4 counts < 200, commonly < 100, who are not on co-trimoxazole prophylaxis. Serological tests have limited use, though if immunoglobulin G antibodies are absent alternative diagnosis is likely. Toxoplasma polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) is highly sensitive and specific, but lumbar puncture may be precluded by midline or tentorial shift. Definitive diagnosis is detection of organisms in tissue by stereotactic computed tomography-guided biopsy, but seldom performed.

First-line treatment is with pyrimethamine (with folinic acid) and sulfadiazine or clindamycin. Prophylaxis is with co-trimoxazole followed by optimisation of HAART. Seronegative patients should not handle cat-litter or eat undercooked meat. The main differential diagnosis is cerebral lymphoma.

Cryptococcal meningitis

Cryptococus neoformans is a ubiquitous yeast, especially in bird droppings. Cryptococcal meningitis / meningoencephalitis tends to present insidiously with fever, headache, visual disturbance, confusion and malaise. Disease is caused by inhalation and dissemination, principally to brain and lungs. Diagnosis is by CSF sampling with positive India ink staining (sensitivity 75–85%), cryptococcal antigen testing (95%) or positive culture (> 95%). First-line treatment is with liposomal amphotericin, usually with flucytosine, for 2 weeks, followed by high-dose oral fluconazole for a further 8 weeks. HAART should be optimised after treatment.

Cytomegalovirus (CMV) encephalitis and retinitis

CMV may cause encephalitis, retinitis or radiculitis.

Progressive multifocal leucoencephalopathy (PML)

PML is caused by reactivation of the polyomavirus John Cunningham (JC) virus, usually with CD4 counts < 50. It produces progressive, unrelenting focal demyelination that may present in a wide variety of ways including localised hemiparesis, aphasia, visual disturbance or ataxia over weeks to months. The JC virus can usually be detected by PCR on CSF and MRI reveals white matter lesions without oedema. HAART is the only treatment.

Other

Other opportunistic infections include: of the brain, herpes simplex and varicella-zoster encephalitis, tuberculous meningitis, tuberculoma, neurosyphilis, nocadia abscesses and aspergillosis; of the spinal cord, varicella-zoster transverse myelitis, tuberculous myelitis and syphilitic myelitis, and infection-related myositis.

HIV-related malignancy

HIV-associated primary central nervous system lymphoma is typically diffuse large B-cell non-Hodgkin's lymphoma resulting from marked immunosuppression and Epstein–Barr virus (EBV). It may present similarly to cerebral toxoplasmosis with headache, focal neurological features and seizures, but is usually subacute. MRI typically reveals a single homogeneously enhancing mass in the periventricular space with mild to moderate surrounding oedema. CSF reveals slightly elevated protein but rarely malignant cells. Histological diagnosis is needed, although a presumptive diagnosis is possible if there is EBV within the CSF. Treatment is unsatisfactory.

Non-AIDS-related disease

Stroke risk is higher in HIV, and may be due to vasculitis from several infections, and HIV itself may provoke vasculopathy with dyslipidaemia. Peripheral neuropathy and occasionally GBS is more common with some HAART drugs through mitochondrial dysfunction.

strongly associated with Epstein–Barr virus, occurs with CD4 counts less than 50 / μl and may be difficult to distinguish from cerebral toxoplasmosis. Seropositivity for *Toxoplasma* antibodies favours toxoplasmosis and detection of Epstein–Barr virus DNA in cerebrospinal fluid suggests primary cerebral lymphoma, but diagnosis may be confirmed by open or stereotactic biopsy. Survival is usually only a few months. Human papillomavirus infection and cervical intraepithelial neoplasia are common in HIV.

Is HIV associated with cardiovascular disease (CVD)?

Multiple factors contribute to increased CVD risk in HIV-infected patients. HIV itself, probably as a consequence of its pro-inflammatory and procoagulatory effects and unfavourable changes in HDL, and HAART, through its metabolic impacts, including insulin resistance and dyslipidaemia, increase the risk of CVD. Protease inhibitors particularly within ART seem to increase the risk of myocardial infarction, but evidence suggests that the relative risk is of less significance than instituting important lifestyle measures. The combination of HAART and statins may increase the risk of complications such as rhabdomyolysis.

What is HIV lipodystrophy?

Up to 30–50% of HIV-infected patients develop a form of lipodystrophy. This may be loss of subcutaneous fat (lipoatrophy) from the face and limbs, and increased central obesity. It is multifactorial, and may be the result of the virus, genetic factors, hypertriglyceridaemia, hypercholesterolaemia or anti-HIV drugs, protease inhibitors especially. Mitochondrial toxicity is mostly nucleoside reverse transcriptase inhibitor related and insulin resistance is linked to protease inhibitors.

How would you test for HIV?

An antibody test in an HIV-infected individual is usually positive within 6–12 weeks after exposure. Antibody tests may be to various core or envelope proteins. Plasma HIV-1 load testing assesses disease progression and response to antiretroviral therapy; various assays include reverse transcriptase polymerase chain reaction. Specific genotypes can be detected by nucleic acid sequencing.

What antiretroviral drugs are available?

This is specialised treatment. The two broad categories of drug are reverse transcriptase inhibitors (RTIs) and protease inhibitors.

Reverse transcriptase inhibitors (RTIs)

These prevent conversion of viral RNA to DNA. Only DNA can be incorporated into the host genome.

- *Nucleos(t)ide RTIs* inhibit reverse transcriptase (RT) and act as DNA chain terminators. They include zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine and tenofovir. Fixed-dose combinations include Combivir (zidovudine and lamivudine), Kivexa (abacavir and lamivudine), Trizivir (zidovudine, abacavir and lamivudine) and Truvada (tenofovir and emtricitabine). Side effects include hypersensitivity reactions, peripheral lipoatrophy, non-alcoholic steatohepatitis and lactic acidosis.
- *Non-nucleos(t)ide RTIs* bind to RT at a site distant to the active site but lead to conformational changes in RT which render it inactive. They include etravirine, nevirapine and efavirenz, available in a triple combination (Atripla). Side effects include hypersensitivity reactions.

Protease inhibitors

These bind competitively to the substrate site of viral protease. They include atazanavir, darunavir, fosamprenavir, indinavir, kaletra, ritonavir, saquinavir and tipranavir. Side effects include gastrointestinal intolerance, dyslipidaemia, accumulation of visceral fat and insulin resistance.

Entry or fusion inhibitors

These interfere with binding, fusion and entry of HIV into host cells. CCR5 inhibitors bind to CCR5 (although as disease advances patients are more likely to harbour viruses that utilise CXCR4 and there is also the potential for CCR5 inhibitors such as Maraviroc to promote switching to CXCR4 utilisation). Enfurvitide binds to gp41 and interferes with its potential to interact with the surface of host cells.

Integrase inhibitors

These target the integrase enzyme and include raltegravir.

What antiretroviral drug treatment strategies are there?

HAART or combination antiretroviral therapy (cART)

The optimum time to start antiretroviral therapy is still not known but HAART, using combinations of at least three drugs for advanced HIV-1 disease, has dramatically improved life expectancy, maintaining viral RNA load at undetectable levels. The lower limit for starting HAART is considered a CD4 count 200/µl because below this the chances of developing an AIDS-defining illness increase dramatically. Potentially, a considerable time span between counts of 350 µ/l and 200 µ/l exists, around 2–5 years given an average viral load.

Effects of HAART / cART on survival

HAART has reduced the incidence of AIDS and AIDS-related mortality by over 40% in the 10-year period 1996 to 2006, with an 80% reduction in mortality in industrialised nations.

HAART side effects

There are concerns about cardiovascular mortality as HAART can induce endothelial dysfunction, increase plasma cholesterol and insulin resistance and possibly cause hypertension. HAART, using three antiviral agents, can suppress viraemia and restore normal CD4 counts and when critical 'cut-off' levels have been exceeded, prophylaxis against opportunistic infections may be stopped (although cellular specific immunity against HIV cannot be adequately restored). HAART also reduces bone density.

Treatment failure and emerging treatments

This is not uncommon and is indicated by an increase in plasma viral load. Failure is more likely with successive regimens. Drug-resistant viruses emerge when susceptibility of the virus to one or more drugs is reduced, and HIV's capacity to mutate vigorously means that stopping HAART even for a short time (often poor concordance) is very bad news. Transmitted drug resistance is now common. The problem is lessened with once-daily combined drug pills.

Why is the profile of opportunistic infection and malignancy similar in patients with HIV to that of patients with renal transplants?

Impaired T-cell and B-cell immunity occurs in HIV, because T-helper lymphocytes are affected. The profile of opportunistic organisms reflects those that normally require T-helper lymphocytes for elimination such as *Mycobacterium*, viruses such as cytomegalovirus and fungi such as *Candida* and cryptococci. Neutrophil-mediated bacterial elimination is still largely intact. Many post-transplant immunosuppressive anti-rejection therapies inhibit interleukin-2, which is central to T-helper lymphocyte proliferation.

What is the state of play with developing HIV vaccines?

Current therapies are able to reduce the viral load to extremely low levels and reduce HIV-driven immune activation, but do not eliminate immune activation entirely. Multiple interactions between gp120 and cellular proteins remain targets for neutralisation and current vaccines with neutralising antibodies, either passively transferred or induced (e.g. stimulated by immunisation with gp120), lack good efficacy.

Antibodies against the gp120-C5 region strongly correlate with slower HIV disease progression, raising the question of a non-neutralising antibody targeting the gp120-C5 domain being used as a vaccine. The other main area of vaccine research is in trying to induce a CD8 cell response through delivery of 'safe' HIV antigens, which might hopefully suppress viral replication and slow disease progression.

Is post-exposure prophylaxis (PEP) important?

Overall it appears to confer a significant reduction in rates of seroconverison, but evidence varies. Following percutaneous injury the risk of transmission of HIV may be around 1 : 300, compared with 1 : 30 for hepatitis C and 1 : 3 for hepatitis B. Factors increasing the risk of transmission include deep injury, visible blood on the device, venepuncture instrumentation, terminal HIV-related illness in the source and possibly viral load in the source, although sources with undetectable viral loads are still capable of infecting others through procedures. The principles for selecting which regimen to use for PEP are similar to those for the treatment of chronic HIV infection: potency, pill burden, dosing schedule and tolerability. The current UK Department of Health guidelines recommend a combination of Truvada (a fixed-dose combination of tenofovir disoproxil and emtricitabine) and Kaletra for 4 weeks as soon as possible after exposure (the use of these agents for PEP is outside their licence.) A health-care worker may not be limited from work and procedures given the low risk of disease acquisition and transfer, but

Table 2.93 Immune deficiency disorders

	Type of immune deficiency	Examples
Primary innate	Complement deficiency	Many complement deficiencies
	Neutrophil deficiency	
Primary adaptive	Common variable immune deficiency	IgA deficiency commonest
	Severe combined immune deficiency	See Case 2.46
	MHC class 1 or 2 deficiencies	'Bald lymphocytes' (very rare)
	X-linked agammaglobulinaemia	B lymphocytes unable to produce immunoglobulin
	Hyper-IgM syndrome	Failure of class switching from IgM-producing B cells
Secondary immunodeficiency	Complement deficiency	Systemic lupus erythematosus Post-infectious glomerulonephritis Bacterial endocarditis
	Immunoglobulin deficiency	B-lymphocyte lymphoproliferative diseases Splenectomy Nephrotic syndrome
	Hypergammaglobulinaemia	Monoclonal lymphoproliferative disease (single B-lymphocyte clone 'crowds out' normal B lymphocytes) Polyclonal hypergammaglobulinaemia (chronic infection/inflammation)
	T-lymphocyte deficiency	T-lymphocyte lymphoproliferative diseases Immunosuppressant drugs HIV infection

HIV, human immunodeficiency virus; Ig, immunoglobulin; MHC, major histocompatibility complex.

cannot be considered HIV negative until a negative HIV test 3 months after completion of PEP. Pre-exposure prophylaxis in preventing sexual transmission has been considered.

How might immunodeficiency arise other than through HIV infection?

Immunodeficiency disorders are outlined in Table 2.93. HIV infection is the most common secondary immunodeficiency. Common variable immunodeficiency is the most common primary antibody deficiency, IgA deficiency the most common type. Complement, neutrophil and primary T-lymphocyte disorders are rare. Non-infectious features such as splenomegaly, granulomata or autoimmunity increase the likelihood of identifying an immunodeficiency. FISHing (full blood count, immunoglobulins, serum complement, HIV test) will detect the most common disorders, and should be undertaken either where recurrent or unusual infections warrant further enquiry or where non-infectious features raise suspicion, analogous to coeliac disease.

CASE 2.40 FALLS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Marianne Wood, aged 74 years

Thank you for seeing this lady who is having an increasing number of falls. She has sustained numerous injuries as a result. Last year she sustained a fractured ankle and humerus. She has no other medical history of note. She denies any loss of consciousness but I wonder if she merits investigation to search for possible causes.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Marianne Wood is a 74-year-old ex-primary school teacher with a lifelong history of falls. She describes herself as a 'clumsy child who always had a tendency to fall', but in adulthood these became more frequent. She now falls approximately monthly. Her husband has adjusted to keeping close to her when walking, ready to break any fall. Last year she fractured her humerus and ankle, required intensive physiotherapy and was unable to write for 2 months or drive for 6 months. She also has a history of a vertebral compression fracture following a fall down stairs. She does not think she loses consciousness when she falls, but does not seem to be able to coordinate her legs, which seem to be clumsy. She has no apparent difficulty with sensation in the feet and legs, is able to sense pain, hot and cold and joint position, and has no apparent difficulty with muscle strength. She has no other medical history of note, and takes no medications. She is extremely worried about having to give up walking, which she loves.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Explore the frequency and time course of falls.** Ask the following:

- When did the falls start?
- How often do they occur – or is it the first fall? (How many in the last 12 months?)
- Are they becoming more frequent?
- Is there a circadian pattern?

■ **Explore the characteristics of falls.** Patients often report one of light-headedness, a sense of the room spinning, or feeling unsteady on their feet (Table 2.94).

Falls may occur:

- *With loss of consciousness* (usually syncope or seizure – Cases 2.41 and 2.42)
- *Without loss of consciousness*, when they may be associated with neuromusculoskeletal instability or disequilibrium (Box 2.93) or they may be purely accidental ('the cat or the carpet'). Vertigo seldom

Table 2.94 Characteristics of the causes of falls

Question	Interpretation
Do you feel light-headed?	Pre-syncope or syncope (Case 2.41)
Is it a sense of the room spinning (rotational or 'to and fro')?	Vertigo (Case 5.49)
Do you feel unsteady on your feet (or wobbly on your legs)?	Disequilibrium

Box 2.93 **Postural equilibrium and disequilibrium**

The body has a small base compared with its height and must constantly take automatic corrective actions to overcome destabilising gravitational forces and maintain postural stability. These actions can produce body sway and limits of sway are known as limits of stability. When the centre of mass is displaced beyond the limits a fall occurs unless there is rapid corrective action, e.g. moving the foot.

Neuromuscular mechanism for postural equilibrium

Balance is a complex sensorimotor process integrated centrally in the brainstem, cerebral cortex, cerebellum and extrapyramidal system, with stabilising sensory information from the vestibular system, vision and somatosensory afferents (e.g. joint position receptors in the lower limbs and spine and touch and pressure receptors in the sole). Somatosensory afferents are most important in postural stability when standing on a hard surface, and vision is important on unstable ground. The vestibular system largely detects head movement and is less perceptive for body sway. Much of this sensory information converges centrally and is used to produce corrective responses at the joints to keep the centre of mass within the limits of body sway, i.e. stabilisation of gaze during head movements and control of posture and equilibrium during movement. Effector pathways include the vestibulo-ocular reflex (stabilises retinal images with head movement) and vestibulospinal pathways to neck and trunk muscles and muscles in the lower limbs.

Postural disequilibrium

Postural unsteadiness or disequilibrium occurs when one of the sensory inputs is perturbed. Normally minor slips or trips provoke rapid motor responses to restore postural equilibrium. Some adaptation can occur to compensate for sensory perturbation, e.g. impaired proprioception compensated for by vision. When sensory compensation is inadequate, motor responses are inadequately evoked and this results in a fall.

Ageing and disequilibrium

Visual acuity, vestibulo-ocular reflexes, vestibular systems, proprioception and cutaneous sensation tend to decline with age or with disuse. These, combined with reduced cerebellar and cerebral processing and increased muscle stiffness, can all contribute to increased body sway over 60 years of age and an increased risk of falls.

Disease and disequilibrium

Many diseases contribute to disequilibrium, e.g. diabetic neuropathy, osteoporosis, stroke, dementia, postural hypotension, cataracts, glaucoma, macular degeneration.

Drugs and disequilibrium

Polypharmacy may contribute to disequilibrium.

Box 2.94 **Falls risk assessment tool**

- History of falling in past year
- Four or more medications
- Stroke or Parkinson's disease
- Balance problems
- Unable to rise from chair or knee height without using arms

provokes loss of consciousness. Most falls are non-syncopal, and in older people are the result of poor mobility and frailty and organ (notably brain, e.g. dementia) vulnerability, or acute illness (intrinsic factors), often combined with extrinsic (environmental) factors. The role of an ageing brain with chronic brain disease and ultimately brain failure is underappreciated as a contributor and cause of falls.

Assessment in patients who are admitted must include cognitive assessment, an electrocardiogram and lying and standing blood pressure if relevant (although most falls on standing are caused by weakness):

- Ask about warning symptoms, whether there is recollection of falling or hitting the floor and whether protective responses to injury are used. Patients may lose consciousness so transiently as to be unaware of having done so. Associated symptoms, such as chest pain, palpitations or breathlessness, should be elicited.
- Ask about direction of fall (in diffuse cerebrovascular disease, for example, gait tends to be upright or even tottering backwards a little, resulting in backward falls).
- Ask how long she is usually on the floor, and how she gets back up.
- Ask about vision and hearing.
- Ask about sensory symptoms.
- Ask about muscle weakness.
- Ask about joint symptoms (pain or swelling).
- Ask if there is vertigo.

■ **Explore environmental factors.** Environmental factors can contribute to falls risk, especially in the setting of disequilibrium. Indoor hazards include bad lighting, steep stairs, lack of edge of step demarcations, lack of rails, slippery floors, loose rugs, pets, grandchildren's toys and cords of telephones and appliances. Outdoor hazards include uneven pavements, streets or paths, lack of safety equipment, snow and ice, traffic and public transportation. A description of footwear should always be elicited.

■ **Assess falls risk.** The falls risk assessment tool predicts a high risk of falls if three or more of the five risks are present (Box 2.94).

People with syncope, recurrent falls in the past year, unexplained high-risk features or disturbance of gait or balance should be offered a specialist multifactorial falls risk assessment with a view to individualised multifactorial intervention. Assessment in outpatient settings should take account of the number and description of falls, environmental and functional assessment, balance and gait assessment, confidence, cognition, medical disorders, past history, medications and osteoporosis risk. The Morse falls risk assessment tool is suited to and validated for inpatients and applies six categories for consideration in arriving at an overall score – history of falling, secondary diagnoses, ambulatory aids, intravenous therapy, gait and mental state. Patients are classified as low, medium or high risk, with management guidance incrementally devised for categories.

Falls are often multifactorial. Chronic disorders causing problems with posture, balance and gait (e.g. peripheral neuropathy, joint disease, stroke, Parkinson's disease) or with cognition may conspire with acute illness (e.g. pneumonia, urinary tract infection, acute confusion or dehydration), drug side effects (e.g. hypotension, sedation or electrolyte disturbances) and environmental hazards. In other words, if a cause of falls is found, assessment should continue.

Patient perspective

Explore any ideas, concerns and expectations about her falls, especially her concerns about stopping work.

Past medical history

Establish the list of injuries sustained.

Drug and allergy history

Important medications contributing to falls risk include:

- All that provoke drowsiness, e.g. antipsychotics, hypnotics, antidepressants, muscle relaxants, opiates, antihistamines, centrally acting antihypertensives
- All that provoke hypotension, e.g. antihypertensives, dopaminergic drugs, anticholinergics, antiemetics
- Others, e.g. antigylcaemics, antiarrhythmics.

Family history

There is occasionally a familial neurodegenerative disorder.

Social history

Enquire about type of accommodation (stairs etc.), environmental hazards, hazardous tasks (e.g. climbing, reaching), functional abilities (mobility, transfer, activities of daily living, e.g. shopping, driving), support services and work.

Discussion

Why is falls assessment important?

Falls assessment is important for numerous reasons, as follows.

Frequency

Falls are common, although most are not reported. One in three people aged over 65 will have at least one fall in a year, and one in two over 80, more if in a care home. Older people should be asked routinely if they have fallen in the last year and about the frequency, characteristics and context of the fall.

Possibility of underlying disorder

Falls may also be the manifestation of an underlying cardiac or neurological disorder.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ There is no apparent loss of consciousness, and the history suggests a problem with neuromusculoskeletal instability, or disequilibrium. She may have a progressive neurological disorder, but the long history suggests a long-standing abnormality and impaired neuronal 'reserve'. New factors increasing her tendency to fall including syncope should still be considered.
- ◆ Osteoporosis risk should be assessed.
- ◆ A full examination, including blood pressure lying and standing, cardiovascular examination (notably for murmurs, and possibly carotid sinus massage with monitoring if no bruits) and neuromusculoskeletal examination (notably cerebellar, peripheral nerve and joint examination) is the next step.
- ◆ Investigations should include routine haematobiochemisty, an electrocardiogram, possible magnetic resonance brain and spine imaging and an osteoporosis dual-energy X-ray absorptiometry scan. Further tests for syncope, including tilt table testing, may be important later.
- ◆ Multifactorial intervention may include strength and balance retraining (e.g. t'ai chi), physiotherapy and occupational therapy assessment. Ear, nose and throat specialists have a role if vestibular disease is suspected. Bone protection should be started.

Consequences

Approximately 3–5% of all falls may result in a fracture, and 10–15% of falls in people over 65 result in serious injury.

Value of intervention

Dedicated falls assessment and intervention services screen for medically treatable causes, assess using a clear and comprehensive pathway and reduce falls risk even where cause is multifactorial by organised exercise programmes and occupational environmental adjustments. Falls assessment and management are all about identifying causes, managing falls risk and reducing fracture risk with appropriate osteoporosis management.

Why are older people at increased risk of falls?

Older people are at increased risk of the features in Box 2.95, and when assessing older people with any condition it is useful to consider the special considerations highlighted by the mnemonic 'RAMPS'.

Box 2.95 **Considerations in assessing older people**

- **R**educed body reserve
- **A**typical presentation
- **M**ultiple medical problems
- **P**olypharmacy
- **S**ocial adversity

Which patients should undergo immediate brain imaging after a fall?

Those with a head injury and:

- Glasgow Coma Scale (GCS) score < 13 when first assessed in the emergency department
- GCS < 15 when assessed in the emergency department 2 hours after the injury
- Suspected open or depressed skull fracture
- Sign of fracture at the skull base (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from ears or nose, Battle's sign)
- Post-traumatic seizure
- Focal neurological deficit
- > 1 episode of vomiting
- Amnesia of events > 30 minutes before impact.

Those who sustained loss of consciousness or amnesia and:

- Age ≥ 65 years
- Coagulopathy (history of bleeding, clotting disorder, current anticoagulation)
- Dangerous mechanism of injury, e.g. pedestrian or cyclist struck by a motor vehicle, occupant ejected from a motor vehicle, fall from > 1 m or 5 stairs.

How might a patient's overall falls risk, gait, balance and strength be assessed?

Overall falls risk

A full examination should include cardiovascular examination, neuromusculoskeletal examination and cognitive assessment, together with assessment of gait and balance in conjunction with a physiotherapist.

Gait

Perhaps the easiest initial assessment of falls risk is the 'get up and go' test. The patient is asked to get up from a chair without using their arms, walk a few paces (6 metres standard), turn around and return to the chair. If this is normal falls risk is low, but if unsteady a full multidisciplinary falls risk assessment is warranted. Impaired 'sit to stand' is probably the most sensitive indicator of falls risk. Walking can also be combined with distraction techniques that involve multitasking such as walking and talking.

Specific balance tests

Methods of assessing balance include: functional reach (how far a patient can reach out without falling, a measure of the range of stability correlating with falls which improves with rehabilitation); body sway (affected mostly by leg strength, peripheral sensation, visual acuity and reaction times and tested by swayometers); step tests, the number of steps to complete a 180° turn increasing with unsteadiness; FICSITT 4 testing (to determine if a patient can stand with feet together side by side, semi-tandem, tandem or stand on one foot). Balance assessment tools include the Berg balance scale and Tinetti balance assessment tool.

Strength

Strength may be assessed by dominant knee extension or hand dynamometry, standing from a chair without hands, gait speed or climbing stairs. Muscle force (strength × speed of contraction) reduces by 20% after a week spent in bed!

List some interventions that reduce falls

Falls research has revealed that the only effective interventions are multidisciplinary, but can reduce up to 30% of falls, and these may include:

- Diagnosing and managing specific causes and risk factors (e.g. cardiac pacing)
- Strength and balance training (physiotherapist)
- Home hazard assessment and intervention (occupational therapist)
- Vision assessment and correction of visual impairment as part of multifactorial intervention
- Footwear assessment
- Medication review and modification/withdrawal.

For inpatients who have sustained a fall, using the Morse management approach the following are performed:

- For those at low risk: documentation of circumstances, communication with the multidisciplinary team and referral as needed, bed kept at lowest setting, appropriate seating provided, items within reach, information leaflets, footwear assessment, environmental safety hazard check, assistance with toilet access if needed
- For those at medium risk: as for low risk plus frequent re-orientation if confused, assessment of risks and benefits of bedrails and types of bedrails, education of patient and carer
- For those at high risk: as for medium risk plus full medical review, patient located in easily observed area, consideration of 1 : 1 nursing, multidisciplinary team involvement, consideration of sensor alarm, consideration of falls team.

List some interventions that cannot be recommended to reduce falls because of insufficient evidence

These include:

- Low-intensity exercise combined with incontinence programmes in older people in extended-care settings
- Group exercise (not a reason to discourage, but little evidence for non-individualised programmes in older people)
- Cognitive/behavioural interventions
- Referral for correction of visual impairment as a single intervention
- Hip protectors in fracture prevention.

Does vitamin D reduce falls risk in older people?

Vitamin D deficiency is common in older people and there is evidence that it impairs muscle strength and possibly neuromuscular function. However, evidence that replacement reduces falls risk is not yet strong. Vitamin D and calcium correction does reduce fracture risk in older people in care.

Which patients might be safely discharged following admission with a fall, and which patients admitted?

Discharge may be considered for patients who are continent, ambulant, rational, able to dress unaided and with safe social circumstances. Patients with injury, an abnormal electrocardiogram or a family history of sudden death should be admitted.

What is rehabilitation?

This is the process of actively restoring function. It is focused and purposeful and aims to improve quality, engagement and participation in life and decrease morbidity and mortality. It is not the same as convalescence, which implies spontaneous recovery. Conditions suitable for rehabilitation are wide ranging and include stroke, fractured neck of femur, heart failure and chronic obstructive disease. Rehabilitation generally starts on acute medical wards and may continue in community hospitals, care settings, outpatient units or at home with the community rehabilitation team.

List some challenges to rehabilitation

- Diagnostic uncertainty (the most important and, surprisingly, common, e.g. confusion in the setting of lung cancer when, for example, brain metastases should first be excluded)
- Constipation
- Incontinence
- Pain
- Sedation
- Pressure sores
- Parietal lobe neglect / inattention
- Cognitive impairment
- Communication problems (including hearing impairment)
- Depression

Which patients should not ideally be referred for rehabilitation?

- Those without a diagnosis
- Those needing complex further investigation
- Those who are medically unstable
- Those awaiting placement

Which patients should be referred for rehabilitation?

Those with a diagnosis and forward plan who are medically stable, who are deemed by the multidisciplinary team to benefit. The referral should not include the phrases ‘acopia’, ‘convalescence’ or ‘awaiting placement’!

Is posture an important element of rehabilitation?

Muscle imbalance (due to neuromusculoskeletal problems, cognitive impairment or reduced activity) leads to disordered posture and sustained segmental (pelvis, hips, knees, feet, ankles, spine) malalignment. Physiotherapists assess posture by examining daily routines, the factors limiting stable posture and inhibiting neutral posture and the effects of posture (e.g. on function, comfort, contracture risk and pressure sore risk). Physiotherapy aims to limit deformity and discomfort and optimise function by, for example, moving all muscles and joints regularly and determining individually optimal bed and seating types.

CASE 2.41 SYNCOPE

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient’s general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Walter Connelly, aged 74 years
> Thank you for seeing Mr Connelly, who collapsed last week. He got up from his chair in the public library and promptly lost consciousness. He recovered rapidly but tells me this has happened before. He has a past medical history of hypertension and takes bendroflumethiazide and losartan. Examination is unremarkable except for an ejection systolic murmur. I would appreciate advice on further management.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP’s letter. You are not required to examine the patient.

Box 2.96 **'Dizziness'**

- Pre-syncope (a sensation of impending loss of consciousness, which may lead to syncope)
- Vertigo (a sensation of movement)
- Disequilibrium or some form of neuromusculoskeletal instability

Box 2.97 **Syncope**

Syncope is a symptom that refers to transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion with loss of postural tone. It is characterised by rapid onset, short duration (typically 20–30 seconds and almost invariably less than 5 minutes) and spontaneous complete recovery.

In some forms there may be a prodromal period in which various symptoms (e.g. light-headedness, nausea, sweating, weakness and visual disturbances) warn that syncope is imminent. Often, however, LOC occurs without warning. Typical syncope is brief. Complete LOC in reflex syncope lasts no longer than 20 seconds. Syncope may rarely be longer, even as much as several minutes. Recovery from syncope is usually accompanied by almost immediate restoration of appropriate behaviour and orientation; however, retrograde amnesia may be more frequent than previously thought, particularly in older individuals. Sometimes the post-recovery period may be marked by fatigue.

'Pre-syncope' refers to symptoms and signs that occur before unconsciousness in syncope.

Patient information

Mr Walter Connelly is a usually well 74-year-old man who last week lost consciousness in the public library. He got up from his chair and with very little warning fell to the floor. He thinks his chest hit the back of the chair as he fell, as he had some discomfort on recovery. He recovered within minutes. He has had two or three similar episodes in the last year. He takes bendroflumethiazide and losartan for hypertension. He has no other past medical history of note, has never smoked, seldom drinks alcohol and lives with his wife in a house with stairs. He drives a car and is keen to continue doing so.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Patients are often referred to outpatient clinics or admitted to hospital with 'dizziness', 'giddiness', 'faintness', 'blackouts' or 'collapse', or attacks of 'altered awareness'. It usually means one of the problems in Box 2.96.

The initial evaluation in syncope should answer three key questions:

1. Is it a syncopal episode or not?
2. What is the aetiological diagnosis?
3. Are there data suggestive of a high risk of cardiovascular events or death?

1. Is it a syncopal episode or not?

■ **Syncope.** Syncope is defined in Box 2.97. Establish the following:

- Was loss of consciousness (LOC) complete?
- Was LOC transient with rapid onset and short duration?
- Did the patient recover spontaneously, completely and without sequelae?
- Did the patient lose postural tone?

If the answers to these questions are positive, the episode was likely to be syncope.

■ **Syncope in the context of transient loss of consciousness (T-LOC).** The term T-LOC (transient, with rapid onset, short duration and spontaneous recovery) encompasses all disorders characterised by self-limited LOC and is divided into traumatic and non-traumatic forms. Concussion usually causes LOC but the presence of a trauma is usually clear. Non-traumatic T-LOC is divided into:

- Syncope
- Seizures
- Psychogenic pseudosyncope
- Rare miscellaneous causes (e.g. cataplexy) or those whose presentation resembles other forms of T-LOC only in rare circumstances (e.g. excessive daytime sleepiness).

■ **Disorders resembling syncope.** Two groups of disorders may superficially resemble syncope:

- Those where consciousness is truly lost, but the mechanism is not global cerebral hypoperfusion, e.g. epilepsy (tone maintained), metabolic disorders (including hypoxia and hypoglycaemia, which will not reverse without treatment), intoxication and trauma induced. Hyperventilation, which is associated with hypocapnia and cerebral vasoconstriction, may result in light-headedness and reduced mental function along with characteristic digital and perioral paraesthesia, but it is only rarely associated with LOC in the absence of an accompanying vasovagal response.
- Those where consciousness is not or only apparently lost, e.g. falls without LOC, drop attacks and psychogenic pseudosyncope. The term drop attack is generally unhelpful, but refers to a sudden fall with the legs giving way without LOC. Contrary to the belief of many doctors, transient ischaemic attacks (TIAs) and cerebrovascular disorders almost never cause syncope (Box 2.98). If a patient has not lost consciousness, but has experienced altered awareness (best corroborated by a witness), then seizure activity seems more likely.

■ **The two main causes of LOC – syncope or seizure ('faint or fit').** Most LOC is due to syncope and not

Box 2.98 **Cerebrovascular disorders and syncope**

Transient ischaemic attacks (TIAs) and cerebrovascular disease

TIAs and cerebrovascular disorders almost never cause syncope and for all practical purposes a TIA provokes a focal deficit without loss of consciousness (LOC) and syncope the opposite.

TIAs related to a carotid artery do not cause transient LOC. When almost all cerebral arteries are occluded, transient obstruction of the remaining vessel subtending a large portion of the brain may extremely rarely affect consciousness only in the standing position, but focal neurological signs are much more prevalent.

TIAs of the vertebrobasilar system can cause LOC, but there are always focal signs, usually limb weakness, gait and limb ataxia, oculomotor palsies, or oropharyngeal dysfunction. Vertebrobasilar insufficiency is mooted as common but is probably rare, much less common than carotid sinus hypersensitivity, for example.

Vascular steal syndromes

Vascular steal syndromes very rarely seduce blood away from the brainstem. 'Subclavian steal' refers to re-routing of blood flow to the arm through the vertebral artery due to stenosis or occlusion of the subclavian artery. A TIA may occur when flow through the vertebral artery cannot supply both the arm and part of the brain, during forceful use of the arm, but a TIA is only likely to be due to steal when it is vertebrobasilar and associated with exercise of one arm and there are no reliable reports of isolated LOC without focal neurological symptoms and signs in subclavian steal. Steal usually affects the left side. It is often asymptomatic.

Migraine

Migraine sufferers have a higher lifetime prevalence of syncope and often frequent syncope, although syncopal and migraine attacks do not usually occur together in these patients.

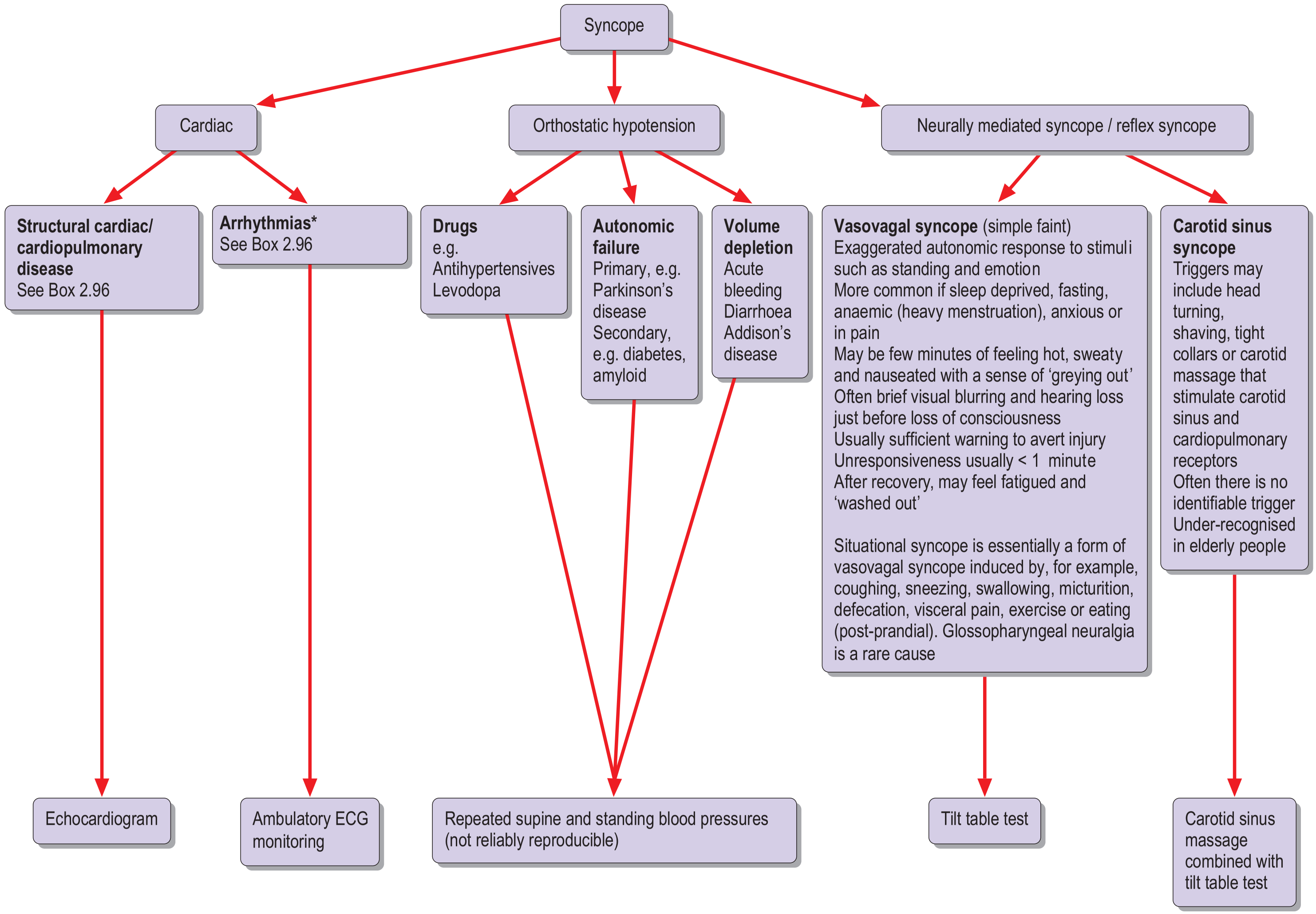
Table 2.95 Differentiating syncope and seizures

	Syncope	Seizure
Prodrome / warning symptoms	Minutes (often 1–10 minutes), e.g. nausea, vomiting, abdominal discomfort, feeling hot or cold or sweaty, light-headedness, blurring of vision	A brief (often 10–30 seconds, and sometimes only 3–4 seconds) aura is typical of a complex partial seizure, e.g. funny smell
Duration of loss of consciousness	Usually < 1 minute (typically 20–30 seconds), and almost invariably < 5 minutes May be longer if recovery thwarted by bystanders propping patient up!	Several minutes (usually 2–5 minutes)
Recovery / first memory	Rapid recovery (wakes at scene) Retrograde amnesia more frequent than previously thought, especially in older people	More prolonged recovery (wakes in ambulance at around 20 minutes)
Skin colour (witness account)	Often 'deathly' pale	Red or blue (cyanosed) in tonic–clonic seizure
Abnormal movements (witness account)	Shaking or jerking can occur with syncope in the form of minor twitching whilst floppy and unconscious or asynchronous myoclonic jerks or small, brief twitching movements ('syncopal seizure' or convulsive syncope) but seldom last more than 15 seconds and always start after the loss of consciousness Automatisms, commonly ascribed to seizures, can also occur during syncope	Rhythmic tonic–clonic movements are common for 1–2 minutes and their onset coincides with the loss of consciousness Automatisms are common and include lip smacking, chewing, mouth frothing, head movements, fumbling movements and grunting
Tongue biting	Biting the tip of the tongue can occur in both syncope and seizures	Biting the side of the tongue, if it occurs, is a robust sign of a generalised tonic–clonic seizure
Incontinence	Can occur (merely reflects full bladder)	Can occur
Eyes	May be open or closed	May be open or closed
Injury	Less likely	More likely

seizures or other causes. Syncope is usually triggered; epilepsy rarely is. The value of a description of episodes (patient or witness) cannot be overstated. Valuable discriminators are given in Table 2.95 but the key is to build up a picture rather than relying on one fact to make the diagnosis. Further, the differentiation can be more difficult in older people.

2. What is the aetiological diagnosis?

■ **Causes of syncope.** Figure 2.13 and Table 2.96 provide a classification based on the pathophysiological causes of syncope. Syncope is common. There is a very high prevalence of first faints in patients between 10 and 30 years. Reflex syncope is the most frequent cause of syncope in any setting. Syncope secondary to cardiovascular


Syncope
Cardiac
Orthostatic hypotension
Neurally mediated syncope / reflex syncope
Structural cardiac/ cardiopulmonary disease
See Box 2.96
Arrhythmias*
See Box 2.96
Drugs
e.g.
Antihypertensives
Levodopa
Autonomic failure
Primary, e.g. Parkinson's disease
Secondary, e.g. diabetes, amyloid
Volume depletion
Acute bleeding
Diarrhoea
Addison's disease
Vasovagal syncope (simple faint)
Exaggerated autonomic response to stimuli such as standing and emotion
More common if sleep deprived, fasting, anaemic (heavy menstruation), anxious or in pain
May be few minutes of feeling hot, sweaty and nauseated with a sense of 'greying out'
Often brief visual blurring and hearing loss just before loss of consciousness
Usually sufficient warning to avert injury
Unresponsiveness usually < 1 minute
After recovery, may feel fatigued and 'washed out'
Situational syncope is essentially a form of vasovagal syncope induced by, for example, coughing, sneezing, swallowing, micturition, defecation, visceral pain, exercise or eating (post-prandial). Glossopharyngeal neuralgia is a rare cause
Carotid sinus syncope
Triggers may include head turning, shaving, tight collars or carotid massage that stimulate carotid sinus and cardiopulmonary receptors
Often there is no identifiable trigger
Under-recognised in elderly people
Echocardiogram
Ambulatory ECG monitoring
Repeated supine and standing blood pressures (not reliably reproducible)
Tilt table test
Carotid sinus massage combined with tilt table test

*Long sinus pauses (3 seconds is of definite significance and an indication for pacing, and shorter pauses with symptoms may be significant during daytime hours) tend to cause pre-syncope or syncope, and syncope may be so brief that patients do not admit to losing consciousness – they may genuinely not believe they did, but equally may not have an adequate explanation for what happened.

Figure 2.13 Types of syncope with examples of diagnoses and tests to help diagnose. ECG, electrocardiogram.

disease is the second most common cause. In younger people orthostatic hypotension is a rare cause of syncope. The most common causes of syncope in older people are orthostatic hypotension, reflex syncope (especially carotid sinus syncope (CSS)), and cardiac arrhythmias.

A sudden cessation of cerebral blood flow for only 6–8 seconds is sufficient to cause complete LOC. Experience from tilt testing shows that a decrease in systolic blood pressure (BP) to 60 mmHg or lower is associated with syncope. Systemic BP is determined by cardiac output and total peripheral vascular resistance, and a fall in either can cause syncope, but a combination of both mechanisms is often present in any type of syncope.

■ **Features helpful in differentiating the causes of syncope.** Initial evaluation is able to define the cause of syncope in 23–50% of patients. Table 2.97 lists clinical features that may suggest a diagnosis.

The '5 Ps' approach to features in the history may also help differentiate causes of syncope (Table 2.98).

3. Are there data suggestive of a high risk of cardiovascular events or death?

Arrhythmias and structural heart disease are major risk factors for sudden cardiac death and overall mortality in patients with syncope (Box 2.99).

Patient perspective

Explore his ideas, concerns and expectations, especially about driving.

Past medical history

Establish the list of injuries sustained. A past medical history of anterior myocardial infarction should alert you to possible ventricular arrhythmias.

Table 2.96 Causes of syncope

Groups of causes	Types	Causes
Reflex syncope (sometimes known as neutrally mediated syncope or neurocardiogenic syncope or neurocardiovascular syncope) Reflex syncope refers to a heterogeneous group of conditions in which cardiovascular reflexes become intermittently inappropriate in response to a trigger, resulting in vasodilatation and/or bradycardia. Reflex syncope may be classified by cause or by response (vasodepressor if hypotension, cardioinhibitory if bradycardia or asystole, mixed if both).	Vasovagal syncope ('common faint')	Emotional stress (fear, pain, instrumentation, blood phobia) Orthostatic stress
	Situational syncope	Respiratory (cough, sneeze) Gastrointestinal (swallow, defecation, visceral pain) Urinary (micturition, post-micturition) Post-exertional (young athletes or older people as an early manifestation of autonomic failure before typical orthostatic hypotension) Post-prandial Laughter Valsalva (brass instrument playing, weightlifting)
	Carotid sinus syncope (also known as carotid sinus syndrome) Carotid sinus hypersensitivity with syncope	
Syncope due to orthostatic hypotension and orthostatic intolerance syndromes Orthostatic hypotension is defined as an abnormal decrease in systolic BP upon standing. In contrast to reflex syncope, in autonomic failure sympathetic efferent activity is chronically impaired so that vasoconstriction is deficient. Orthostatic intolerance refers to symptoms and signs in the upright position due to a circulatory abnormality.	Primary autonomic failure	Parkinson's disease with autonomic failure Parkinsonian syndromes with autonomic failure, e.g. Lewy body dementia, multiple system atrophy Pure autonomic failure Idiopathic orthostatic hypotension
	Secondary autonomic failure	Diabetes Amyloidosis Uraemia Alcohol Spinal cord disease
	Volume depletion or redistribution	Haemorrhage Sepsis Diarrhoea, vomiting Hypoadrenalism Prolonged bed rest
	Drug-induced	Alcohol Antihypertensives Diuretics Levodopa

Table 2.96 Causes of syncope—cont'd

Groups of causes	Types	Causes
Cardiac syncope (cardiovascular) Arrhythmias are the most common cardiac causes. In sick sinus syndrome, the sinoatrial node is damaged and syncope is due to long pauses caused by sinus arrest or sinoatrial block and a failure of an escape mechanism. These pauses are most frequently encountered when an atrial tachyarrhythmia suddenly stops (brady–tachy syndrome). The more severe forms of acquired atrioventricular block (Mobitz II block, 'high grade', and complete atrioventricular block) are most closely related to syncope, as cardiac rhythm may be dependent on often-unreliable escape pacemaker sites with delay before these pacemakers begin to 'fire' and relatively slow rates. Bradycardia also prolongs repolarisation and predisposes to polymorphic ventricular tachycardia, especially torsade de pointes. Several drugs can cause brady- and tachyarrhythmias. Structural cardiovascular diseases cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output.	Arrhythmias	Bradycardia Sinus node dysfunction (including bradycardia / tachycardia syndrome) Atrioventricular conduction system disease Device malfunction Tachycardia Supraventricular Ventricular (idiopathic, secondary to structural heart disease or to channelopathies) Drug-induced
	Structural disease	Cardiac Valve disease Acute myocardial infarction / ischaemia Hypertrophic cardiomyopathy Cardiac masses (atrial myxoma, tumours) Pericardial disease / tamponade Congenital anomalies of coronary arteries Prosthetic valve dysfunction Other Pulmonary embolus Acute aortic dissection Pulmonary hypertension

BP, blood pressure.

Drug and allergy history

Diuretics and angiotensin modulators can provoke syncope by postural hypotension, and can derange electrolytes.

Family history

Relevance here is unlikely, but ask about sudden cardiac death.

Social history

Ask about driving.

Discussion

What is the mechanism of reflex syncope?

The basic problem is afferent pathways feeding to brainstem cardioinhibitory and vasodepressor centres leading to syncope by hypotension (vasodepressor) and variable bradycardia or asystole (cardioinhibitory).

Stimulation of the brainstem medullary vasodepressor region may follow activation of cardiac C-fibre mechanoreceptors (hypovolaemia causing reduced preload, Valsalva manoeuvre), cardiopulmonary baroreceptors (coughing, sneezing, carotid massage), cranial nerves (glossopharyngeal neuralgia), the cerebral cortex (anxiety, panic, pain) or gastrointestinal or genitourinary mechanoreceptors (defecation, micturition). In hypovolaemia and emotional states such as pain and anxiety the starting point may be increased sympathetic tone, leading to hypercontractility (increased ionotropy and chronotropy) of the volume-depleted left ventricle and subsequent stimulation of C-fibres.

In all cases the common endpoint of receptor activation is compensatory parasympathetic (vagal) enhancement with bradycardia or transient asystole and decreased sympathetic tone with peripheral vasodilatation, reduced venous return, reduced cardiac filling, decreased cardiac output and cerebral hypoperfusion.

SUMMARY BOX – ASSESSMENT AND PLAN

- Symptoms are consistent with reflex syncope, although orthostatic hypotension may be a cause, and is a much more common cause than aortic stenosis, which has to be very severe to cause syncope and then often associated with other symptoms. However, the gradient across the valve in aortic stenosis is exacerbated by angiotensin receptor blockers.
- Echocardiography is important on account of the murmur, as is ambulatory electrocardiogram monitoring. The limitations of diagnostic tests such as electrocardiogram monitoring are that capturing a spontaneous event is unusual and a causal relationship between a diagnostic abnormality and syncope is often presumptive. The cause of syncope remains unknown in a substantial proportion of patients.
- Further cardiac investigation might be helpful because it is unclear whether his chest pain was secondary to trauma.
- A tilt table test will be helpful.
- If postural recordings confirm orthostatic hypotension, his antihypertensives should be weaned.
- The evidence base for investigations in syncope is limited, without gold standards (the diagnostic yield of tests being measured indirectly by the reduction of recurrence of events after administration of therapy as indicated by the test). Further, the evidence basis for many treatments is also limited.

Table 2.97 Features helpful in diagnosing the cause of syncope

Reflex syncope	Absence of heart disease Long history of recurrent syncope After sudden unexpected unpleasant sight, sound, smell, pain or sensation Prolonged standing or crowded, hot places Nausea and vomiting During a meal or post-prandial After exertion (though beware cardiac syncope) With head rotation or pressure on carotid sinus (shaving, tight collars, tumours, head turning)
Orthostatic hypotension (OH)	After standing up Temporal relationship with start or change of dose of vasodepressor drugs leading to hypotension Prolonged standing, especially in crowded, hot places Presence of autonomic neuropathy or Parkinsonism Standing after exertion Various clinical syndromes of orthostatic intolerance are recognised: **Classical OH** This is defined as a decrease in systolic BP ≥ 20 mmHg and in diastolic BP ≥ 10 mmHg within 3 minutes of standing. It occurs commonly in old age, with autonomic failure, drugs or hypovolaemia. **Initial OH** This is characterised by a BP decrease immediately on standing of > 40 mmHg. BP then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (< 30 seconds). It may occur in old or young people, and in CSS. **Delayed (progressive) OH** This is not uncommon in older people, probably due to age-related impairment of compensatory reflexes and stiffer hearts, and characterised by a slow progressive decrease in systolic BP with upright posture. The absence of a bradycardiac reflex (vagal) differentiates delayed OH from reflex syncope although delayed OH may be followed by reflex bradycardia. **Postural orthostatic tachycardia syndrome** This mostly occurs in young women, presenting with severe orthostatic intolerance, but not syncope, with very marked heart rate increases (> 30 bpm or to > 120 bpm) and instability of BP. **Reflex OH** This may be triggered by standing, and occurs mostly in healthy young people.
Cardiac syncope	Cardiac syncope such as prolonged sinus pauses may be so brief that patients genuinely do not believe they lost consciousness, although they may not have an adequate explanation for what happened. **Electrocardiogram abnormalities that may suggest arrhythmic syncope** Bifascicular block (left or right bundle branch block with left anterior or posterior fascicular block) Other intraventicular conduction abnormalities (QRS duration ≥ 0.12 seconds) Mobitz I second-degree atrioventricular block Asymptomatic sinus bradycardia (< 50 bpm), sinoatrial block or sinus pause ≥ 3 seconds in the absence of negatively chronotropic drugs Non-sustained ventricular tachycardia Pre-excitation QRS complexes Long or short QT intervals Early repolarisation Right bundle branch block pattern with ST elevation in leads V1–3 (Brugada syndrome) Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggesting arrhythmogenic right ventricular dysplasia Q waves as legacy of myocardial infarction **Electrocardiogram abnormalities diagnostic of arrhythmic syncope** Sinus bradycardia with a heart rate < 40 bpm Repetitive sinoatrial block or sinus pauses > 3 seconds in the absence of negatively chronotropic medications Mobitz II second- or third-degree block Alternating right and left bundle branch block Rapid ventricular or supraventricular tachycardia Pacemaker malfunction

BP, blood pressure; bpm, beats per minute; CSS, carotid sinus syncope.

What tests might be useful in syncope?

Initial evaluation of T-LOC requires careful history, examination (including orthostatic BP measurements) and electrocardiogram. Based on these findings, additional assessment may include:

- Electrocardiographic monitoring
- Echocardiography when there is known or suspected heart disease
- Orthostatic challenge (lying-to-standing orthostatic test and/or head-up tilt testing) when syncope is

Table 2.98 The '5 Ps' approach to diagnosing the cause of syncope

Features		Suggested diagnosis
Precipitants	Warm or crowded environments	Vasovagal syncope
	Specific situation	Situational syncope
	Dehydration	Orthostatic hypotension
	Head movements, tight collars, shaving	Carotid sinus syncope
	During exercise, no obvious precipitant	Cardiac syncope
Prodrome	Light-headedness, dizziness, disturbances (including blurring, enhanced brightness, tunnel vision), hearing disturbances (including impaired hearing, crackles, tinnitus)	Vasovagal syncope Orthostatic hypotension
	Nausea, sweating, abdominal pain	Vasovagal syncope
	None	Vasovagal syncope in older people Cardiac syncope
	Chest pain, breathlessness, no prodrome	Cardiac syncope
Palpitations		Cardiac syncope
Position	Prolonged standing	Vasovagal syncope Orthostatic hypotension
	Sudden change in posture	Orthostatic hypotension
	Supine	Cardiac syncope
Post-event phenomena	Nausea, vomiting, fatigue	Vasovagal syncope
	Immediate complete recovery	Any, common in arrhythmia

Box 2.99 **High-risk features in syncope**

Severe structural or coronary artery disease

- Heart failure, low ejection fraction
- Previous myocardial infarction

Clinical features

- Syncope during exertion or supine
- Palpitations at the time of syncope
- Family history of sudden cardiac death

Electrocardiogram features

- Inadequate sinus bradycardia (< 50 beats / min) or sinoatrial block in the absence of negative chronotropic medications or physical training
- Bifascicular block (left or right bundle branch block with left anterior or posterior fascicular block)
- Other intraventicular conduction abnormalities (QRS duration ≥ 0.12 seconds)
- Non-sustained ventricular tachycardia
- Pre-excitation QRS complexes
- Prolonged or short QT intervals
- Right bundle branch block pattern with ST elevation in leads V1–3 (Brugada syndrome)
- Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggesting arrhythmogenic right ventricular dysplasia

Comorbidities

- Severe anaemia
- Electrolyte disturbance

related to the standing position or there is suspicion of a reflex syncope

- Carotid sinus massage (CSM) in patients > 40 years.

Electrocardiographic monitoring (non-invasive and invasive)

As a general rule, electrocardiographic monitoring is indicated only when there is a high pre-test probability of identifying an arrhythmia associated with syncope. However, in patients > 40 years with recurrent syncope, without significant structural heart disease and with a normal electrocardiogram, an arrhythmia, usually asystole, is present during syncope in up to 50%. In-hospital monitoring (in bed or telemetry) is warranted only when the patient is at high risk. The gold standard for diagnosis of syncope is when correlation between symptoms and a documented arrhythmia is recorded. The presence of some asymptomatic significant arrhythmias, defined by prolonged asystole (≥ 3 seconds), rapid supraventricular tachycardias (≥ 160 beats / min for > 32 beats) or ventricular tachycardias, is considered by some diagnostic. The absence of documentation of an arrhythmia during a syncopal episode allows exclusion of an arrhythmia as a reason for syncope.

Electrocardiographic monitoring is traditionally undertaken with conventional 24–48-hour, or even 7-day, Holter recorders (for episodes occurring at least weekly). However, since in most patients symptoms do not recur during the monitoring period, the true yield of Holter in syncope may be very low. Event recorders are external devices applied by the patient when symptoms occur. Whilst useful in investigating palpitations they have no role in the evaluation of syncope. External loop recorders (for episodes occurring every 1–2 weeks) are connected to the patient through cutaneous patch electrodes and are suitable when there is warning of symptoms, with an increased diagnostic yield compared with Holter monitoring; they have a loop memory that continuously records and deletes electrocardiograms, but when activated by the patient, typically after a symptom has occurred, 5–15 minutes of pre-activation electrocardiographic monitoring is stored and can be retrieved for analysis. Implantable loop recorders (for episodes occurring less frequently) are implanted subcutaneously under local anaesthesia and have a battery life of up to 36 months.

Echocardiography and other imaging

Echocardiography plays an important role in risk stratification on the basis of left ventricular ejection fraction. In the presence of structural heart disease, other tests to evaluate a cardiac cause of syncope should be performed. Echocardiography identifies the cause of syncope in very few patients when no more tests are needed (e.g. aortic stenosis, atrial myxoma, tamponade). Transoesophageal echocardiography, computed tomography, and magnetic resonance imaging may be performed in selected cases (e.g. aortic dissection and haematoma, pulmonary embolism, cardiac masses, pericardial and myocardial diseases, congenital anomalies of coronary arteries).

Other cardiac investigations

Electrophysiological studies may be indicated in syncope with ischaemic heart disease (unless there is an established indication for an implantable cardiac defibrillator), bundle branch block where other tests have not revealed another cause, palpitations where other tests have not revealed a cause, selected patients with Brugada syndrome, arrhythmogenic right ventricular dysplasia or hypertrophic cardiomyopathy and people in high-risk occupations where knowledge of cause could have a major impact.

Exercise-induced syncope is infrequent. Exercise testing should be performed in patients who have experienced episodes of syncope during or shortly after exertion.

Cardiac catheterisation techniques (e.g. coronary angiogram) should be carried out in suspected myocardial ischaemia or infarction or ischaemia-driven arrhythmias.

The role of endogenous adenosine release in triggering some forms of syncope due to otherwise unexplained paroxysmal atrioventricular block (the so-called 'adenosine-sensitive syncope'), diagnosed by adenosine triphosphate testing, remains unclear.

Orthostatic challenge tests

Changing from supine to upright position produces a displacement of blood from the thorax to the lower limbs that leads to a decrease in venous return and cardiac output. In the absence of compensatory mechanisms, a fall in BP may lead to syncope.

Active standing

This is used to diagnose different types of orthostatic intolerance.

The sphygmomanometer is adequate, used to measure BP supine and during active standing for 3 minutes, as initial evaluation when orthostatic hypotension is suspected. Continuous beat-to-beat non-invasive pressure monitoring may be helpful in cases of doubt. The test is diagnostic when there is a symptomatic fall in systolic BP from a baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, or a decrease in systolic BP to < 90 mmHg. It may be considered diagnostic with these values even in asymptomatic people.

Orthostatic hypotension may be worse after getting out of bed and not present in clinic. It may be delayed and only occur after a period of standing, diagnosed by a head-up tilt table test. Whilst the terms postural hypotension and orthostatic hypotension are often used interchangeably, postural hypotension strictly refers to a drop immediately after standing whilst orthostatic hypotension may be delayed, often so in older people. Ambulatory BP recordings may be helpful in identifying abnormal diurnal patterns. These recordings may also help identify supine or nocturnal hypertension in treated patients.

Tilt table testing

This is an orthostatic challenge test used when reflex syncope is suspected. It should ideally be performed with beat-to-beat monitoring of BP – the basic problem with vasovagal syncope is a drop in BP, chased very quickly, within seconds, by a dramatic drop in heart rate. The clinical situation corresponding to tilt testing is reflex syncope triggered by prolonged standing. However, this test can also be positive in patients with other forms of reflex syncope and in patients with sick sinus syndrome.

Prolonged standing is estimated to lead to an effective 700 ml drop in plasma volume in healthy adults. This may cause a slight compensatory rise in heart rate, but ultimately this paradoxically slows in patients with vasovagal attacks.

A modern tilting protocol comprises 20 minutes of passive 70° head-up tilt followed by glyceryl trinitrate (GTN) spray. Exaggerated responses with progressive hypotension without bradycardia are an effect of GTN and more common in older people. Patients are supine for 5

Table 2.99 Tilt table testing responses and treatments – reflex syncope

Type	Response	Definition	Treatment
Type 1	Mixed cardioinhibitory and vasodepressor	Heart rate falls but not to < 40 bpm	Cardiac pacing (less effective in mixed with important vasodepressor component)
Type 2A	Cardioinhibitory without asystole	Heart rate < 40 bpm for > 10 seconds	Cardiac pacing (considered for CSH more than vasovagal syncope)
Type 2B	Cardioinhibitory with asystole	Asystole > 3 seconds with symptoms	Cardiac pacing (considered for CSH more than vasovagal syncope)
Type 3	Vasodepressor	Fall in SBP of > 50 mmHg with symptoms HR does not fall by more than 10% of its peak at the time of syncope	More difficult to treat and evidence for treatments lacking Compression hosiery Salt tablets Fludrocortisone

bpm, beats per minute; CSH, carotid sinus hypersensitivity; HR, heart rate; SBP, systolic blood pressure.

minutes before the tilt and fast for 2 hours before the tilt. Tilts are best performed in the morning, in a quiet, darkened room to reduce sympathetic drive.

Upright tilting in people without reflex syncope reduces venous return, but subsequent baroreceptor stimulation and increased α- and β-adrenergic tone averts syncope. In reflex syncope there is decreased venous return, but sympathetic tone increases with the stimulation of C-fibres leading to stimulation of the medullary vasodepressor region, sudden reduction in sympathetic tone (vasodilatation) and concurrent increase in vagal tone (bradycardia) causing syncope. In other words, a BP drop may be chased rapidly by an inappropriate heart rate drop. The prodromal phase occurs at a systolic BP of around 90 mmHg then systolic BP rapidly falls and precedes a decrease in heart rate. Approximately 50% of patients with a positive baseline test become negative on repeat testing.

The endpoint of tilt testing is the induction of either reflex hypotension / bradycardia or delayed orthostatic hypotension associated with syncope or pre-syncope. When a reflex is induced, according to the predominance of vasodepressor or cardioinhibitory components, the responses have been classified as cardioinhibitory, vasodepressor or mixed (Table 2.99).

Tilt testing is not usually needed in patients whose reflex syncope is diagnosed by clinical history. A negative test does not exclude reflex syncope. It has no value in assessing treatment efficacy. It is safe. It is usually combined with carotid sinus testing.

Carotid sinus massage (CSM) for carotid sinus hypersensitivity (CSH) and carotid sinus syncope (CSS)

Pressure at the site where the common carotid artery bifurcates – the anterior margin of the sternocleidomastoid muscle at the level of the cricoid cartilage (angle of the jaw where the carotid pulse is maximally felt) – produces a slowing in heart rate and fall in BP – the *cardioinhibitory* component due to parasympathetic overactivity causing sinus bradycardia or atrioventricular block and the *vasodepressor* component due to sympathetic underactivity causing loss of vascular tone and hypotension independent of heart rate changes. In some individuals there is an exaggerated reflex response to carotid sinus stimulation. A ventricular pause lasting > 3 seconds and / or a fall in systolic BP of > 50 mmHg defines CSH. When associated with spontaneous syncope, CSH defines CSS.

Diagnosis of CSS requires the reproduction of spontaneous symptoms during 10 seconds of sequential right and left CSM performed supine and erect, under continuous monitoring of heart rate and periodic measurement of BP, permitting better evaluation of the vasodepressor component. In up to 30% of patients, an abnormal reflex is present only in the upright position, especially in those with vasodepressor responses. Highly sensitive patients may be symptomatic with minimal provocation (even listening for bruits!). CSH is a common finding in older male individuals, but patients with CSS is more unusual. CSS is exceptional in patients < 40 years old.

Neurological complications from CSM are reported with an incidence of 0.17–0.45%, and CSM should be avoided in patients with a carotid bruit (unless imaging has excluded significant stenosis), previous stroke, myocardial infarction in the past 3 months or a history of sustained ventricular tachycardia. It should always be performed with recorded monitoring to avoid unnecessary repeat testing if positive to prove bradycardia or asystole and persuade the cardiology team to consider a pacemaker! A carotid ultrasound is safe practice prior to CSM where there is concern about possible carotid atheroma.

How may reflex syncope be treated?

Education

In general, initial treatment comprises education about awareness and avoidance of triggers (e.g. hot crowded environments, volume depletion), early recognition of prodromal symptoms, and performing manoeuvres to abort the episode (e.g. supine posture, physical counterpressure manoeuvres). If possible, triggers should be addressed directly, such as cough suppression in cough syncope. Careful avoidance of agents that lower BP (including alpha blockers, diuretics and alcohol) is important.

Physical counterpressure manoeuvres (PCMs)

PCMs are emerging as a new front-line treatment of reflex syncope. Isometric PCMs of the legs (leg crossing and gluteal clenching), or of the arms (hand grip and arm tensing), are able to induce a significant BP increase during the phase of impending reflex syncope that allows the patient to avoid or delay losing consciousness in most cases.

Tilt training

In highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress, the prescription of progressively prolonged periods of enforced upright posture (so-called 'tilt training') may reduce syncope recurrence.

Drugs

Many drugs have been tested in the treatment of reflex syncope, most with disappointing results. Fludrocortisone has been widely used in adults with reflex syncope, but there is no trial evidence to support this. Beta blockers have been presumed to lessen the degree of ventricular mechanoreceptor activation owing to their negative inotropic effect in reflex syncope, but the theory is not supported by evidence and they are not now recommended. Paroxetine was shown to be effective in one placebo-controlled trial but not confirmed in other studies.

Pacing

Pacing plays a small role in reflex syncope, unless severe spontaneous bradycardia is detected during prolonged monitoring, but appears to be beneficial in CSS.

How may orthostatic hypotension and orthostatic intolerance be treated?

Treating cause

Thorough assessment to identify possible causes should consider volume status, diseases that can affect the autonomic nervous system, and drugs. Dehydrated patients should be considered to have hypoadrenalism until a short synacthen test proves otherwise, particularly if there is hypoglycaemia or hyponatraemia, although these are late disturbances. Euvolaemic patients may be on antihypertensives or other hypotension-inducing agents, or may have long-standing diabetes or primary autonomic failure as in Parkinson's disease, multi-system atrophy, or primary autonomic failure. Orthostatic hypotension with tachycardia suggests hypovolaemia, but failure to produce heart rate compensation suggests autonomic dysfunction.

Education

Education as outlined for reflex syncope can improve orthostatic symptoms markedly, even though the rise in BP is relatively small (10–15 mmHg); raising the standing BP just enough to be within the autoregulatory zone can make a substantial functional difference. Expansion of extracellular volume is important. In the absence of hypertension, patients should be instructed on sufficient salt and water intake, targeting 2–3 litres of fluid per day and 10 g of NaCl. Rapid cool water ingestion is reported to be effective in combating orthostatic intolerance and post-prandial hypotension.

Physical counterpressure manoeuvres (PCMs)

PCMs such as leg crossing and squatting should be encouraged in patients with warning symptoms able to perform them.

Sleeping position and gravitational measures

Sleeping with the head of the bed elevated prevents nocturnal polyuria, maintains more favourable distribution of body fluids, and ameliorates nocturnal hypertension. Gravitational venous pooling in older patients can be treated with abdominal binders or compression stockings.

Drugs

In contrast to reflex syncope, the α-agonist midodrine is a useful addition to the first-line treatment in some patients with chronic autonomic failure. There is no doubt that midodrine increases BP in both supine and upright posture and that it ameliorates the symptoms of orthostatic hypotension. Midodrine (2.5–20 mg, three times daily) has been shown to be effective in three randomised placebo-controlled trials. Caution is needed with prostatism. Fludrocortisone (0.1–0.3 mg once daily – higher doses usually limited by hypokalaemia) is a mineralocorticoid that stimulates renal sodium retention and expands fluid volume. The evidence in favour of fludrocortisone is from small studies. Less frequently used treatments, alone or in combination, include desmopressin in patients with nocturnal polyuria, octeotride in post-prandial hypotension, erythropoietin in anaemia, pyridostigmine, use of walking-sticks, frequent small meals, and judicious exercise of leg and abdominal muscles, especially swimming.

How would you manage orthostatic hypotension in heart failure?

More challenging are patients with heart failure or fluid overload and postural hypotension. This may be the result of heart failure drugs or simply a failing heart. Here, the above drug therapies are contraindicated (other than cautiously withdrawing antihypertensive heart failure drugs because of balance of risk) and it is counterintuitive to prescribe furosemide and fludrocortisone. Salt tablets and midodrine should also be used with extreme caution in patients with supine hypertension or a history of stroke.

How would you manage orthostatic hypotension with supine hypertension?

Some patients have supine hypertension and orthostatic hypotension; theoretically it may be possible to re-sensitise cerebral autoregulation such that antihypertensives can be used without orthostatic hypotension but in practice it may be necessary to accept hypertension and reduce falls risk by withdrawing drugs.

How may cardiac syncope be treated?

Specialist cardiology input is usually needed for further investigation and consideration of pharmacological or device therapy. Sinus pauses ≥ 3 seconds (less if symptomatic) warrant consideration of pacing.

What driving regulations are there after syncope?

For Group 1 (private) drivers:

- For unexplained syncope with low risk of recurrence there are no restrictions but absence of a prodrome, occurrence whilst driving, or the presence of severe structural heart disease warrants restriction and investigation. Frequently syncope versus other diagnoses has not been established without doubt and patients should be advised to inform the driving licensing authority.
- For reflex syncope there are no restrictions after a single mild episode but recurrent or severe symptoms must first be controlled.
- For cardiac syncope successful treatment must first be established for arrhythmias.

Group 2 (professional) drivers have steeper restrictions.

CASE 2.42 SEIZURES

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Julian Green, aged 40 years
>
> Thank you for seeing Mr Green who had an episode of collapse last week. He was found confused in the kitchen by his wife, and had cut his head on a kitchen unit. She called the ambulance but he was recovering by the time it arrived. He had bitten his tongue but there was no incontinence. He was discharged from the emergency department following a normal computed tomography brain scan. He remembers going into the kitchen but then nothing until the ambulance arrived.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Julian Green is a usually well 40-year-old taxi driver who recently had an episode of collapse at home. He remembers walking into the kitchen at around 14.00 hours but then has no recollection of events until an hour later, waking up in an ambulance. He sustained a laceration on the side of his head from a kitchen unit, together with a bite to the side of his tongue. He was taken to the emergency department where he received five sutures and underwent a computed tomography (CT) brain scan that he was told was normal. He felt slightly drowsy for the remainder of the day. He lives with his wife and does not drink or smoke or take illicit drugs. He had an episode 3 months previously of collapsing in the garden, but without injury. He had been at home alone, had spent five hours gardening on a hot day and felt a rubbery taste in his mouth before falling to the ground; he had come to after what seemed like minutes and attributed the episode to 'heat-stroke'.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Diagnosis and differential diagnosis.** Diagnosis of seizures is primarily clinical, based on a clear history from the patient and from an eyewitness. Syncope is the most common alternative in a wide differential diagnosis (Case 2.41) that also includes non-epileptic attack disorder, panic attacks, drop attacks, migraine, narcolepsy, daydreaming, transient global amnesia, vertigo and movement disorders. The history should include details of attacks, of any warning or prodrome and of the aftermath. The context is important: attacks occurring from standing or following exercise and with warning are likely to be syncopal; epilepsy is more likely if sitting, lying or sleeping, if in clusters with little or no warning and stereotyped.

Frequent attacks of long duration, with normal intellectual function in between, are likely to be non-epileptic.

■ **Recognise the phases of a seizure.** There are, potentially, three phases to a seizure (although they may not be present), details of which you should try to elicit (Table 2.100).

Patient perspective

Explore his concerns about driving, explaining that unexplained loss of consciousness poses a risk to himself and other road users.

Past medical history

Ask about predisposing and precipitating factors (Table 2.101).

Drug and allergy history

Some drugs can alter seizure threshold.

Family history

Relevance here is unlikely.

Social history

This is mandatory, not least with respect to occupation (operating machinery or working at heights), sport (e.g. diving, swimming alone) and driving.

SUMMARY BOX – ASSESSMENT AND PLAN

- Partial complex seizures seem likely.
- An electroencephalogram and magnetic resonance imaging scan are warranted.
- He should be advised not to drive and to inform the Driver and Vehicle Licensing Agency.
- An anti-epileptic drug should be started after further assessment.

Discussion

How would you define a seizure?

A seizure is a clinically apparent episode of aberrant, paroxysmal electrical activity within the brain.

What is the risk of having a seizure?

The lifetime risk of having a seizure is around 5%, and around 30–50% of such people will have a recurrence.

How would you define epilepsy?

Epilepsy refers to a tendency to recurrent seizures, has a prevalence of 0.5–1% in the developed world and has a wide range of causes. It is therefore more helpful to think of 'the epilepsies' rather than 'epilepsy'. Recent advances include better classification, refined imaging techniques and molecular genetics, and new medical and surgical treatments.

How are seizures classified?

Seizures may broadly be classified as focal, generalised or unclassifiable. Epilepsy is classified in a similar way, although the term focal is increasingly used rather than partial.

How is epilepsy classified?

Epilepsy classification is complex because it may be considered in terms of clinical manifestations and electroencephalogram (EEG) features (focal or generalised), by cause (somewhat confusingly idiopathic or primary, which implies a genetic cause, cryptogenic, which implies no known cause, and symptomatic, which implies a known cause), by syndrome or by trigger. Classification is important to determine prognosis and choose appropriate medication. A simplified version of the International League Against Epilepsy (ILAE) classification is shown in Table 2.102.

Idiopathic tonic–clonic generalised seizures tend to have a genetic basis, no known cause and a structural lesion is unlikely. They are to be benign and relatively easy to control, and to arise in teenage years.

Epilepsy of adult onset is most commonly focal and acquired and the prognosis variable, depending on cause. New onset acute symptomatic seizures should always prompt a search for causes and acute symptomatic seizures are common in the elderly, often in the context of an encephalopathy. Systemic disorder causes include drugs/withdrawal, metabolic disturbance (hypoglycaemia, hypocalcaemia, hyponatraemia), endocrine disease, organ failure and porphyria. Central nervous disease triggers include stroke, head injury, infection (meningitis, encephalitis, abscess), cerebral vasculitis, cerebral venous thrombosis, hypertensive encephalopathy and hypoxia. These seizures are usually generalised tonic–clonic seizures, and require brain imaging, sometimes cerebrospinal fluid analysis, and a low index of suspicion of herpes viral encephalitis with treatment with acyclovir, particularly when there has been a prodrome of flu-like illness or headache for a few days, followed by confusion, before the seizure.

Seizures arising from sleep are most likely to be focal. In about a fifth of cases, a structural brain lesion can be identified; others are considered cryptogenic and a structural cause presumed. Genetic focal epilepsies with a specifically identified genetic mutation are rare.

Epilepsy and learning disability are commonly associated, up to 60% of patients with severe learning disability having epilepsy.

In view of the high rate of misdiagnosis, all patients with suspected seizures should be referred quickly to an epilepsy specialist.

What is non-epileptic attack disorder?

Non-epileptic attacks are very common. They are often dramatic, tend to be generalised, often where there is reported in the case-record 'known epileptic now in status', and without the tell-tale persuasive signs of genuine seizures that include pupil dilatation and lack of resistance

Table 2.100 Three phases of a seizure

Phase	Characteristics	Seizure type
Initial phase or aura	Aura, the subjective experience of seizure discharge, can take almost any form; it is a seizure, or part of a seizure, not a prodrome **Somatosensory** Olfactory / gustatory, e.g. tastes Auditory hallucinations, e.g. foreign voices, peculiar noises Visual, e.g. alterations in shape, size or distance of objects Vertigo (very rare) **Psychic** Déjà vu (sense of familiarity with the situation) Jamais vu (failure to recognise surroundings) Depersonalisation (sense of being detached from self) Derealisation (sense of the surroundings feeling unreal) Autoscopy (sense of seeing the body from the outside) **Autonomic auras** Include changes in heart rate, piloerection, sweats, nausea and strange rising epigastric sensation	**Generalised – convulsive** Aura may be very brief
		Generalised – absence or atonic drop attack No warning Atonic drop attack can cause serious injury
		Partial – complex Aura common (notably in temporal lobe epilepsy) May be protracted, sometimes even for days Occasionally spouses see changes days beforehand, and dogs sense something amiss! May be no warning at all
Loss of (or altered) awareness or consciousness	Patient usually inaccessible, failing to respond to other people or with altered awareness; not necessarily convulsive	**Generalised – myoclonic, clonic, tonic or tonic–clonic** Usually lasts minutes Eyes may roll up, pupils dilate and 'wide-eyed stare' Period of rigidity (tonic phase) with or without cyanosis followed by generalised jerking (clonic phase) during which may be tongue biting, incontinence and vomiting
		Generalised – absence Brief (5–10 seconds) absence in which patient appears to be daydreaming Eyelids may flutter Rapid recovery
		Partial – simple Abnormal jerks, e.g. jerk of one arm resulting from abnormal discharge in contralateral motor gyrus
		Partial – complex Abnormal behaviour and automatisms (repetitive stereotyped semi-purposeful movements), e.g. lip smacking and chewing May last seconds, minutes, hours or rarely days!
Post-ictal	Patient may be aware something has happened, but be confused afterwards	**Generalised** May remain confused for some hours afterwards Amnesia for its events Aphasia may be possible
		Partial – complex Sometimes recollection of bizarre alterations of perception, e.g. visuospatial experiences such as micropisa or macropsia (a sense of the world shrinking or enlarging), altered time perception and 'magical thinking' Variety of experiences almost endless, and may culminate in psychiatric referral but: symptoms in complex partial seizures reflect the lobe involved; symptoms are much less common than psychiatric disorders with psychotic symptoms; violent behaviour rare in seizures and invariably non-directional

Table 2.101 Predisposing and precipitating factors for seizures

Predisposing factors	Precipitating or trigger factors
Birth injury	Sleep deprivation
Head injury	Alcohol or drug use
Stroke	Flashing lights
Space-occupying lesions	Stress
Meningitis / encephalitis	Menstruation

Table 2.102 Classification of epilepsy

Category	Examples
Special syndromes (not epilepsy)	Febrile convulsions Provoked seizures, e.g. alcohol withdrawal Isolated (single) seizures
Generalised epilepsy	Primary or idiopathic epilepsy (subclassified by age of onset, e.g. childhood absence epilepsy, juvenile myoclonic epilepsy, epilepsy with tonic–clonic seizures only) Cryptogenic epilepsy (subclassified by age of onset, e.g. epilepsy with myoclonic absence seizures) Symptomatic (non-specific syndromes or specific syndromes)
Focal epilepsy	Idiopathic Cryptogenic Symptomatic (temporal, frontal, parietal, occipital)
Epilepsies undetermined	Focal or generalised

to eye-opening; however, whilst they can be bizarre and obvious, they can also sometimes be remarkably difficult to recognise. There is no underlying structural brain disturbance or 'bad brain', and these attacks are more common in females, those with a history of self-harm and poisoning, those with previous unexplained symptoms, and those with a history of experiencing child-abuse or from dysfunctional family backgrounds. Fifty per cent of 'status epilepticus' presenting to emergency departments is a non-epileptic attack disorder.

Conversely, some real seizures do not look like seizures. These include frontal seizures, and non-convulsive status epilepsy, the latter more common in older people in whom it can appear as confusion, and with complex partial attacks, sometimes apparent only because of automatisms such as fidgeting or oro-facial automatisms. An EEG will diagnose these; in children absences are more common.

What is transient global amnesia?

This is often in the differential diagnosis of a seizure. During an attack, patients function almost normally but have no recollection of what has happened. They might go to the shops, or the golf course, or wander around town, and then drive home without recollection of their activities over the past few hours. An attack generally lasts under 24 hours, and seldom recurs. The cause is uncertain, but it does not seem to be due to seizure activity or a cerebrovascular disturbance, and it probably reflects aberrance in the temporal lobe.

Which investigations may help in diagnosing epilepsy?

Investigations may help to confirm diagnosis and establish a cause.

Serum prolactin levels, once considered useful, are not recommended to distinguish between epileptic and non-epileptic attacks.

An EEG should not be used 'to exclude epilepsy' and used only if there is a strong clinical suspicion of epilepsy; false-positive 'non-specific' EEG abnormalities are very common, particularly in the elderly, whilst around 50% of people with epilepsy have normal inter-ictal EEGs. The main value in an EEG is to confirm a clinical suspicion of epilepsy and assist in classification. Normal EEG waveforms include alpha (normal, 8–12 Hz), beta (fast normal or abnormal, > 12 Hz), theta (slow, usually abnormal, 5–7 Hz) and delta (very slow, abnormal, < 4 Hz). Common abnormalities include sharp / spiked complexes that may indicate epilepsy, focal abnormalities and diffuse slow wave activity seen in encephalitis and diffuse cerebrovascular disease with dementia. EEGs are not generally useful for monitoring epilepsy. Video-EEG recording may be used either where the diagnosis is in doubt (most commonly where non-epileptic attacks are suspected) or as part of detailed work-up for epilepsy surgery.

Imaging (magnetic resonance imaging (MRI) unless contraindicated or unavailable) should always be performed if the epilepsy starts in the first 2 years of life or in adults, since a structural lesion is more likely. Others should be scanned if the history suggests focal seizures. MRI is most likely to detect covert structural abnormalities and will detect mesial temporal and hippocampal sclerosis. Functional MRI can be used whilst a patient is performing a task.

Following a first seizure, when would you consider immediate or inpatient neuroimaging and management?

'Red flags' warranting rapid investigation, which may include neuroimaging and lumbar puncture as well as relevant blood tests, are listed in Box 2.100.

When would you consider anti-epileptic drug (AED) treatment after a first seizure?

This has been long debated. Reassuring clarification comes from the MESS study, which showed that starting treatment after a first seizure reduces recurrence at 2 years but

Box 2.100 **Red flags warranting urgent investigation**

- New focal neurology
- Persistent altered mental state
- Fever (but note that temperature and white cell count may rise after a seizure)
- Persistent headache (but many patients have a mild headache)
- Recent head injury
- History of malignancy
- Human immunodeficiency virus
- Anticoagulated patients or patients with a bleeding tendency
- Age > 40 years

has no benefit on longer term remission rates, and leads to no reduction in sudden unexpected death in epilepsy (SUDEP) compared with deferred treatment (after two or more seizures). Further results from the MESS study identified three features associated with a high risk of seizure recurrence that might warrant immediate treatment. These were:

- The existence of a pre-existing neurological disorder
- An abnormal EEG
- Occurrence of two or more seizures at presentation.

Provoked seizures are those caused by an acute metabolic disturbance, most commonly alcohol or drugs, or by an acute brain injury. Any metabolic disturbance should be corrected and short-term benzodiazepines used for alcohol withdrawal and delirium tremens. Prophylactic AED treatment is not indicated following an acute brain injury and provoked seizures should be treated for a short time only.

How would you treat epilepsy?

Anti-epileptic drugs (AEDs)

Most AEDs inhibit excitatory neurotransmitters such as γ-aminobutyric acid (GABA). The history of AEDs started with bromides in the 1850s and phenobarbital and phenytoin in the first half of the 20th century. The 1960s and 1970s saw sodium valproate (valproate) and carbamazepine become standard treatments, which they still are. From the early 1990s the so-called 'newer' AEDs began to appear, such that the choice of AED following a new diagnosis of epilepsy is now complex and affected by age, comorbidity, concomitant medication, possibility of pregnancy and the individual's epilepsy classification. As such, it should be made by a specialist. AEDs and their indications and cautions are listed in Table 2.103.

Enzyme-inducing AEDs may cause an asymptomatic rise in liver function tests that does not signify liver dysfunction and does not require action. Interactions occurring between individual AEDs are best managed in the neurology clinic, but important interactions also occur with other drugs.

Enzyme inducers (carbamazepine, phenytoin and phenobarbital) are metabolised by the cytochrome P450 system; warfarin and digoxin are two notable examples where drug levels may fall following initiation of an enzyme-inducing AED. Enzyme-inducing AEDs may also exhibit autoinduction whereby, after several weeks of initially successful therapy, seizure frequency increases owing to increased metabolism of the AED. AEDs are susceptible to drug interactions as well as causing them. Potent P450 enzyme inhibitors such as erythromycin, clarithromycin and cimetidine can lead to significant increases in serum AED levels. Common interactions are listed in Table 2.104.

AED choices

AED choices are given in Table 2.105.

Monotherapy

Monotherapy should be the aim, starting with a low dose and increasing slowly until either seizures remit or adverse effects emerge. A single drug should be increased to the maximum tolerated level before abandoning it for another. AEDs should be tailored to epilepsy classification, lifestyle and possible side effects. If epilepsy is unclassifiable, a broad-spectrum drug such as sodium valproate should be chosen. Valproate remains the best combination of efficacy and tolerability for generalised epilepsies. The multicentre SANAD study suggested lamotrigine has non-inferior efficacy and is better tolerated than carbamazepine as monotherapy for focal-onset epilepsies and it may become the preferred choice. Once an effective monotherapy AED is found (two or three may be tried), over 70% of patients achieve full seizure control.

Combination therapy

If the first AED does not work then alternative monotherapy is considered. Up to 30–40% of such patients may continue to have seizures, often because of underlying damage such as hippocampal sclerosis. Treatment resistance should prompt review of the diagnosis and concordance with treatment, but trial and error is needed to find the optimal regimen – make change, wait and see, make change, wait and see … . Combination therapy is considered when treatment with two first-line AEDs has failed or when the first well-tolerated drug improves control but fails to produce seizure freedom at maximum dosage. Here, combinations of two drugs may be tried. Sodium valproate and lamotrigine work well together, but evidence for effectiveness of combinations is lacking. Polypharmacy can be counterproductive, sometimes producing exacerbations in seizures and worsening side effects. It should be remembered, however, that misdiagnosis is common. Those with refractory epilepsy despite combination AED therapy may be referred to a neuroscience centre for reappraisal of diagnosis and a minority benefit from epilepsy surgery or vagal nerve stimulation.

Table 2.103 Anti-epileptic drugs (AEDs)

AED		Indications	Side effects* and comments
Older AEDs	Sodium valproate	Focal or generalised	Acute toxicity with ataxia or diplopia Thrombocytopenia Weight gain Hair loss Fine tremor Hepatic dysfunction
	Carbamazepine	Focal	Acute toxicity with ataxia or diplopia Blood dyscrasias Syndrome of inappropriate antidiuretic hormone
	Phenytoin	Focal or generalised	Acute toxicity with ataxia or diplopia Blood dyscrasias Gum hypertrophy, hirsutism and coarse features Peripheral neuropathy Cerebellar atrophy
Newer AEDs	Lamotrigine Blocks fast-inactivated sodium channels	Focal or generalised	Rash, the reason for slow titration Stevens–Johnson syndrome, toxic epidermal necrolysis
	Oxcarbazepine Blocks fast-inactivated sodium channels	Focal	Often used where carbamazepine not tolerated Stevens–Johnson syndrome, toxic epidermal necrolysis
	Lacosamide Blocks slow-inactivated sodium channels	Focal	Prolonged cardiac conduction
	Gabapentin Blocks high-voltage-activated calcium channels	Focal	Ataxia Confusion Nightmares
	Pregabalin Blocks high-voltage-activated calcium channels	Focal	
	Levetiracetam Modulates synaptic vesicle protein 2A	Focal or generalised	A novel, effective AED with a unique mode of action, fewer side effects or interactions, frequently used as add-on treatment
	Topiramate Various actions on multiple targets	Focal or generalised	Renal calculi Glaucoma Reversible cognitive slowing
	Zonisamide Various actions on multiple targets	Focal	Renal calculi
	Vigabatrin		The first newer AED but caused visual field constriction, and seldom used
	Tiagebine		Experience still limited
	Eslicarbazepine		Experience still limited
	Retigabine		Experience still limited

*Side effects common to all AEDs include somnolence, nausea and neurotoxicity (e.g. ataxia, visual disturbance) following initiation; numerous AEDs lower bone mineral density.

Do you have any concerns about AEDs in acute illness?

As well as interactions with other drugs, patients with epilepsy admitted to hospital may be declared 'nil by mouth'. Efforts should be made to administer the patient's usual AEDs via the enteral route such as by nasogastric. Most AEDs have relatively short half-lives and omission can quickly lead to refractory seizures or status epilepticus, especially with barbiturate withdrawal. Phenytoin, phenobarbital, valproate, levetiracetam and most benzodiazepines are available intravenously; lamotrigine,

Table 2.104 Important interactions with anti-epileptic drugs (AEDs)

Drugs	Potential effects
Phenytoin / carbamazepine (enzyme inducers)	Reduces levels of warfarin, digoxin, oestrogens, progesterones, beta blockers, calcium channel blockers, corticosteroids, tricyclic antidepressants, valproate, lamotrigine, topiramate Levels increased by erythromycin, clarithromycin, cimetidine, amiodarone, diltiazem, verapamil, omeprazole, isoniazid, acetazolamide Levels reduced by rifampicin
Valproate (enzyme inhibitor)	Increases levels of lamotrigine (smaller doses and slower titration of lamotrigine are required if used with valproate), carbamazepine, phenobarbital, benzodiazepines, warfarin Levels increased by cimetidine, erythromycin, clarithromycin, isoniazid Levels reduced by rifampicin
Lamotrigine	Levels reduced by oestrogens, progesterones, carbamazepine, phenytoin, phenobarbital, rifampicin Levels increased by valproate
Antipsychotics / antidepressants (SSRIs, tricylic, possibly MAOIs)	May inhibit anticonvulsant effect of AEDs (increase seizure risk) with implications for AED doses

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 2.105 Anti-epileptic drug (AED) choices

	Drugs used in focal-onset epilepsies	Drugs used in generalised epilepsies
First line	Carbamazepine or lamotrigine are first line Levetiracetam, oxcarbazepine or valproate should be tried if carbamazepine or lamotrigine are ineffective or not tolerated If the first AED is ineffective, an alternative from the above five should be considered	Valproate* is first line If valproate is unsuitable lamotrigine should be considered (may exacerbate myoclonic epilepsy) Carbamazepine and oxcarbazepine may be considered
Adjunctive treatment for refractory seizures	If first-line treatments are ineffective or not tolerated, adjunctive treatments include carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topirimate If adjunctive treatment is ineffective or not tolerated, other AEDs may be considered with tertiary specialist advice, e.g. eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabitran zonisamide	If first-line treatments are ineffective or not tolerated, adjunctive treatments include clobazam, lamotrigine, levetiracetam, valproate or topirimate

*Avoid as first choice AED in women of childbearing age when possible.

carbamazepine and topiramate are not. Carbamazepine is available for short-term use as a suppository but with limitations in dose and efficacy. Early involvement of a neurologist is encouraged to choose an alternative AED.

Is monitoring of AED levels needed?

Routine measurement of AED levels is not necessary, except perhaps for phenobarbital and phenytoin. Doses are adjusted on the basis of clinical information such as seizure frequency and adverse effects, and not on the basis of AED levels. Some patients achieve seizure freedom with AED levels below the 'normal' range and some tolerate levels above the 'normal' range without clinical toxicity. One scenario definitely inviting routine AED level monitoring is status epilepticus; a common contributor to treatment failure in status epilepticus is subtherapeutic phenytoin. Levels may also be measured if non-concordance is suspected or with signs of toxicity.

What are the important considerations with AEDs and pregnancy?

Women with epilepsy who wish to or may become pregnant need to be counselled on the increased risk of major congenital malformation associated with AEDs, and indeed epilepsy itself. In the UK a register has been in operation since 1996 that forms an ongoing prospective study of all AEDs. Current evidence suggests valproate (6.2%) and polytherapy (6.0%) are associated with the highest major congenital malformation rates; carbamazepine (2.2%) is little worse than the background population rate (1–2%). Rates for the newer AEDs are not yet clear. All women of childbearing age should take folic acid 5 mg daily to help minimise risk. When choosing an AED for women of childbearing age valproate is generally avoided where possible, lamotrigine a commonly used alternative. However, when already pregnant it is often better not to attempt changing AEDs as it may be too late and exposes the mother and child to the additional risks of seizures.

What are the important considerations with AEDs and contraception?

The most common drug interaction of AEDs is the effect of enzyme inducers (carbamazepine, phenytoin and phenobarbital) on the combined oral contraceptive pill (COCP). These drugs increase hepatic metabolism of the COCP and so a higher dose of oestrogen is advised. At least 50 µg and as much as 100 µg daily may be required but no preparation in the UK contains more than 40 µg in one tablet and so multiple tablets are required and this still does not guarantee against contraceptive failure. Progesterone-only pills are even more affected by enzyme inducers and not recommended. A special situation exists with lamotrigine where the reverse phenomenon is seen and the COCP can reduce lamotrigine levels and an increase in lamotrigine dose is required. Twelve-weekly medroxyprogesterone injections (Depo-Provera) are not affected by AEDs, but this is not so for progesterone implants. Intrauterine devices are unaffected by AEDs.

What are the important considerations with AEDs and older people?

Older people have the highest incidence of new diagnoses of epilepsy and the majority have cryptogenic focal epilepsy. The incidence of side effects is higher, multiple concomitant medications increase the potential for drug interactions, renal and hepatic function decreases with age, and cognitive impairment with compliance failure is important. However, seizures in the elderly are often easily controlled and AED choice is often determined less by best efficacy and more by fewest side effects and drug interactions. Valproate remains a common choice, but lamotrigine and levetiracetam are increasingly popular, and lower than usual doses are required. Ataxia and cognitive impairment associated with carbamazepine, phenytoin or valproate may be wrongly attributed to cerebrovascular disease or dementia as a cause of falls. Carbamazepine and oxcarbazepine also cause hyponatraemia.

What do you know about post-stroke epilepsy?

This is very common. EEG is generally unhelpful because of the high rate of abnormalities that do not correlate with epilepsy. Whether or not to treat a first seizure is without an evidence base, and many physicians would treat pragmatically for a month and some for longer given that a structural abnormality has occurred. Valproate is a broad-spectrum, well-tolerated AED and is often first choice by physicians, although National Institute for Health and Clinical Excellence guidelines recommend carbamazepine as first choice for partial-onset seizures. However, the ILAE recommends gabapentin or lamotrigine as first-line monotherapy for partial-onset seizures, and gabapentin is the only AED specifically evaluated in post-stroke epilepsy, with some evidence emerging for levetiracetam. These latter agents may demonstrate fewer side effects (e.g. bone health) and drug interactions (e.g. with antiplatelet agents or anticoagulants) of relevance to older people.

What do you know about status epilepticus?

This is uncommon in chronic epilepsy, and is usually seen in the context of an acute cerebral illness. Prognosis reflects the cause. Early status epilepticus produces discrete tonic–clonic seizures, with a typical EEG, during which there are commonly tachycardia, hypertension, fever and hyperglycaemia. Late status epilepticus must be avoided with early and aggressive treatment as it has a high mortality; it is characterised by decreased consciousness and fragments of myoclonus with a periodic EEG, together with bradycardia, hypotension, hypoglycaemia, acidosis, pulmonary oedema, multi-organ failure and rhabdomyolysis.

How would you treat status epilepticus?

An approach to treatment in status epilepticus is shown in Box 2.101.

Box 2.101 **Treatment of status epilepticus**

- Secure airway
- Give oxygen
- Assess cardiac and respiratory function
- Secure intravenous access (and take blood for electrolytes, liver function, calcium, glucose, clotting and anti-epileptic drug (AED) levels)
- Give lorazepam 4 mg intravenously or diazepam 10 mg intravenously; repeat after 10 minutes if no response (rectal diazepam or buccal midazolam could be used if intravenous access is delayed)
- Measure blood gases
- Give thiamine (alcohol suspected) or 50% glucose solution (hypoglycaemia)
- In established epilepsy give usual AED orally, nasogastrically or intravenously within 30 minutes
- In new-onset epilepsy or if seizures continue give fosphenytoin (18 mg/kg phenytoin equivalent), up to 150 mg/min with electrocardiographic monitoring or phenytoin 18 mg/kg
- After around 30 minutes of status epilepsy, autoregulatory mechanisms fail and cerebral hypoxia occurs which may stop seizure activity, although electrical activity persists. If seizures last more than minutes ITU care may be necessary, with anaesthesia with electroencephalographic monitoring and midazolam, phenobarbital, propofol, or thiopentone being most commonly used
- For non-convulsive status epilepsy usual AEDs should be augmented or reinstated and intravenous lorazepam or diazepam considered

When would you consider AED withdrawal and what are the implications?

Drug withdrawal should be discussed with patients who have been seizure free for at least 2 years. Withdrawal is associated with an increased risk of seizure recurrence, and the extent of risk is influenced by the duration of seizure freedom, seizure type (juvenile myoclonic epilepsy high risk), occurrence of one or more seizures after the start of treatment and whether the mono- or polytherapy is used. EEG abnormalities are a poor risk indicator. Drugs should be withdrawn slowly and one at a time.

The Driver and Vehicle Licensing Agency strongly advises that patients withdrawing from medication should stop driving during the period of withdrawal and for 6 months afterwards.

After at least 2 years of seizure freedom this might be considered. Factors to discuss include risks and fears of seizure recurrence, driving, employment and concerns about long-term treatment. Withdrawal should be gradual, usually over a few months.

What do you know about SUDEP?

Patients with epilepsy have a mortality rate two to three times greater than the general population, and causes include the underlying disease in symptomatic epilepsy, SUDEP, status epilepticus, suicide, treatment, and accidents due to seizures. SUDEP is more likely with frequent seizures.

What patient information is important in epilepsy?

Patients need information on a range of issues including driving, employment, medication, first aid, sport and leisure, benefits, contraception, pregnancy and fertility. Risk advice is essential with respect to driving, occupation, sport and use of hot water at home (e.g. turning on the cold tap first as burns units frequently admit patients with epilepsy). Common sense advice would apply in situations such as working at heights or underground, near open water, with hot ovens or open fires, with high-voltage/open circuit electricity, operating heavy machinery or moving vehicles with chemicals. All patients should be advised against swimming in deep water or alone and having baths alone. Special considerations include preconception advice, pregnancy and lactation.

CASE 2.43 DELIRIUM AND ACUTE CONFUSION

Candidate information

Role

You are a doctor on the medical ward. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Mrs Henrietta Smyth, aged 79 years

Mrs Smyth has confusion and a possible urinary tract infection on the basis of blood and protein on urinalysis. Her sodium was 109 mmol/l on a recent admission and is self-correcting slowly following withdrawal of bendroflumethiazide. Her abbreviated mental test score remains 4/10. Her daughter is present with her, and would like to report the presentation and background to you.

Yours sincerely

Please take a history from the daughter (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case. You are not required to examine the patient.

Patient information

Mrs Henrietta Smyth, your mother, is a 79-year-old woman who has been admitted to hospital with confusion and a possible urinary tract infection. There have been numerous previous episodes of confusion, and this is her third admission to hospital in the last year. Mrs Smyth has lived alone in her three-bedroom house since being widowed 2 years ago but your major concern is that she appears to have hallucinations at home. She often talks about children behind the curtains in her bedroom at twilight. When challenged about this, her response is not denial but more matter of fact – that they can be a nuisance and often refuse to leave when she wants to go to sleep. The hallucinations seem to settle each time she comes into hospital when she simply reports that 'that is not happening any more'. Mrs Smyth has a history of hypertension, for which she was on treatment, but no other significant past medical history. She also takes diazepam at night to improve sleep. You are very concerned that when well enough for discharge the hallucinations will return and that her safety is increasingly challenged and precarious.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Delirium (sometimes called 'acute confusional state') is a clinical syndrome characterised by disturbed consciousness, cognitive function or perception, which has an acute onset and fluctuating course. It is a common but serious and complex clinical syndrome associated with poor outcomes. Delirium requires a three-step assessment approach:

- Recognition of cognitive impairment
- Distinguishing delirium from dementia
- Consideration of causes.

■ **Recognise that the patient has cognitive impairment.** A patient admitted to hospital with chest pain justifiably has an electrocardiogram taken. A patient in whom cognitive impairment is possible should have that defined. Terms such as vague or poor historian are not acceptable. The abbreviated mental test score (AMTS; Box 2.102) is a rudimentary test of cognition, a score of < 8/10 implying cognitive impairment. It does not diagnose delirium or dementia but can alert physicians to a need for further assessment.

An even briefer assessment (AMT4) is also acceptable – age, date of birth, location, year).

Box 2.102 **Abbreviated mental test score (AMTS; abbreviated 10-item Roth–Hopkins – or later Hodkinson – test)**

- Age
- Time (hour)
- Year
- Name of place
- Recognition of two people, e.g. relative and doctor
- Date of birth
- Date of First World War (or Second)
- Monarch
- Counting back from 20 to 1
- Five-minute recall – of '42 West Street'

■ **Distinguish delirium from dementia.** Delirium is a common reason for admission to hospital and a common occurrence in patients admitted to hospital for another reason. Patients may present as 'confused', 'vague', 'a poor historian', 'uncooperative', 'rambling', 'incoherent', 'anxious' or 'tearful'. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for delirium are as follows:

- Develops over a *short period* and *fluctuates* over the course of the day (a relative or carer account is essential)
- Disturbance of consciousness with reduced ability to focus, sustain or shift attention (that delirium is an *attention disorder* is key)
- *Altered cognition* (memory or language deficit, disorientation or perceptual disturbance) not better explained by dementia (although delirium is more likely in people with dementia and is a predictor of future dementia)
- The history, examination or tests show that the condition is a direct consequence of a medical condition, intoxication or substance withdrawal.

The *Confusion Assessment Method* (Table 2.106) is a validated screening tool that applies four features (a diagnosis of delirium requiring the presence of 1 and 2 and either 3 or 4). Whereas disturbances in mood, memory, coherent thinking and executive function may be common to delirium or dementia, inattention characterises delirium (e.g. inability with spelling 'WORLD' backwards or reciting days or months backwards or serial 7s).

■ **Establish possible causes.** Often causes are multifactorial. AEIOU-STRANGE (Table 2.107) is a useful mnemonic checklist for considering causes of acute confusion (delirium) and subacute confusion or 'subacute encephalopathy'.

Table 2.106 Confusion assessment method for diagnosing delirium

1. Sudden onset and fluctuating course	Acute confusion develops over hours to days. Ask relatives about changes from the patient's normal baseline and whether behaviour fluctuates during the day.
2. Inattention	There is reduced ability to focus, sustain or shift attention. Establish whether the patient is distractible, and has difficulty keeping track of what is said or following commands.
3. Disorganised thinking	Establish whether the patient's thinking is muddled or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas or unpredictable switching from subject to subject.
4. Altered level of consciousness (clouding, with reduced clarity of awareness of environment)	Patients may have *hyperactive* delirium with heightened arousal and considerable psychomotor activity such as plucking bedclothes, restlessness, agitation or non-directed aggression or *hypoactive delirium* and be quiet, apathetic, sleepy and withdrawn, and this can easily be missed or diagnosed as depression, especially as such patients can be disengaged, often refusing to eat or drink, yet polite when approached; speech may be incoherent and not follow what is being said. They have a mixture of the two subtypes of delirium. Establish whether the patient is alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stuporose (difficult to arouse) or comatose (unarousable). Most patients display a mixture of features within the extremes of hypoactivity and hyperactivity. Reversal of the normal wake–sleep cycle is common.

Table 2.107 Causes of acute or subacute confusion

	Cause	Time course	Possible investigations
A	Acute or acute on chronic or chronic (dementia)	Acute or subacute worsening of dementia	Collateral history
E	'ETOH' (alcohol)	Acute toxicity or withdrawal Chronic	History
I	Iatrogenic or over-the-counter drugs	Usually acute May be subacute or chronic	Drug history
O	Oxygen – hypoxia / hypercapnia; reflection of cardiac or respiratory disturbance	Acute	Arterial blood gases Electrocardiogram Chest X-ray
U	Urea / biochemical / metabolic derangements: Uraemia Hepatic encephalopathy Hyponatraemia Hypercalcaemia Hypothyroidism	Acute or subacute	Urea and electrolytes Creatinine Liver function tests Calcium Thyroid function tests and autoantibodies (may be euthyroid)
S	Sepsis and infection (non-neurological)	Acute	Urinalysis and culture Chest X-ray Blood cultures Other tests directed by assessment, e.g. ultrasound for biliary obstruction / sepsis
	Sepsis and infection (neurological): Viral, e.g. herpes simplex, varicella-zoster Bacterial, e.g. Lyme disease, syphilis, abscesses HIV opportunistic infection (e.g. cerebral toxoplasmosis, cryptococcal meningitis, cytomegalovirus, progressive multifocal leucoencephalopathy, tuberculous, nocardia) or dementia Prion diseases / transmissible spongiform encephalopathies	Acute or subacute encephalopathy or rapidly progressive dementia (HIV, prion disease)	Neuroimaging Cerebrospinal fluid analysis Serology
T	Trauma (e.g. subdural haematoma)	Acute, subacute or chronic	Neuroimaging
	Tumour: Primary Metastatic Paraneoplastic (e.g. limbic encephalitis)	Acute (e.g. seizure) or subacute / rapidly progressive dementia	Neuroimaging Paraneoplastic autoantibodies
	Temperature (hypothermia/fever)	Acute	Temperature
	Thyroid function	Subacute or chronic	Thyroid function tests / autoantibodies
	Thiamine deficiency	Subacute or chronic	Alcohol history
	Toxicity: Alcohol Substance misuse Poisons, e.g. lead, carbon monoxide poisoning from leaking gas fires (improves on admission to hospital), mercury, venoms	Acute, subacute or chronic	Requires index of suspicion
	Thrombotic thrombocytopenic purpura	Acute, subacute or chronic	Blood film
	Transient global amnesia	Acute	History
R	Retention (urinary or faecal)	Acute	Bladder scan, per rectal examination, abdominal X-ray

Table 2.107 Causes of acute or subacute confusion—cont'd

	Cause	Time course	Possible investigations
A	Autoimmune and inflammatory disease: Acute disseminated encephalomyelitis Cerebral lupus (lupus or associated antiphospholipid syndrome) Cerebral sarcoid Behçet's disease Demyelination Anti-NMDA receptor encephalitis associated with NMDA autoantibodies against NR1 and NR2 subunits of the glutamate NMDA receptor (highly treatable) Autoimmune (non-paraneoplastic) limbic encephalitis associated with voltage-gated potassium channel autoantibodies and occasionally glutamic acid decarboxylase autoantibodies (responds to immunosuppression) Cerebral vasculitis including giant cell arteritis	Often subacute	Autoimmune tests
N	Non-convulsive epilepsy / epileptic amnesia	Often subacute	Electroencephalogram
G	Glucose derangement (hypo / hyperglycaemia)		Blood glucose
E	'Eccentricity'		

HIV, human immunodeficiency virus; NMDA, N-methyl-D-aspartate.

Patient perspective

It is important, when talking with relatives, to involve patients where appropriate to do so. Here, of course, you should elicit her daughter's concerns about safety.

Past medical history

Risk factors for delirium include:

- Age 65 years or older
- Cognitive impairment (past or present) and / or dementia
- Current hip fracture
- Severe illness (a clinical condition that is deteriorating or is at risk of deterioration).

Drug and allergy history

Thiazide diuretics are a common cause of hyponatraemia. Benzodiazepines are a common cause of confusion. Almost any drug can cause confusion, common ones being sedatives, opioids, corticosteroids, anticholinergics (tricyclics, antihistamines, oxybutynin theophyllline), dopaminergic drugs, antidepressants, anti-epileptic drugs and digoxin.

Family history

Relevance here is unlikely.

Social history

It is essential to establish the extent of involvement from the daughter and other relatives or carers.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ Hyponatraemia is a likely acute cause (beware of diagnosing urinary tract infection with only blood and protein on urinalysis).
- ◆ First steps are to ban bendroflumethiazide and diazepam and treat possible infection.
- ◆ Further investigations for hyponatraemia depend upon whether it corrects.
- ◆ The visual hallucinations are worrying, and suggest a possible background dementia such as Lewy body dementia. A 'dementia' screen including brain imaging is probably warranted.
- ◆ Although delirium is traditionally seen as transient, 30–60% of patients have clinically significant new cognitive impairment several weeks later, and there is an increased risk of dementia, functional decline and need for care placement. It is not clear whether delirium is a marker of reduced cognitive reserve or a trigger for brain damage; it may be both.
- ◆ Assuming subsequent investigations are normal, involving the community psychiatric team at discharge would be sensible, and of course the daughter's concerns are perfectly legitimate and may prompt psychiatric review whilst her mother is an inpatient.

Discussion

What is the pathogenesis of delirium?

The pathogenesis of delirium is poorly understood, but in addition to a background of ageing-related changes in the brain and neurodegenerative disease (e.g. Alzheimer's disease), biological and structural factors are key. What is very important is that delirium is an independent risk factor for morbidity and mortality, and although often occurring on a background of a vulnerable brain, it seems to be a factor in progression to a more vulnerable one, and dementia.

Biological factors

Three important acute factors that are likely to contribute are the role of particular neurotransmitters, inflammation and disruption of the hypothalamic–pituitary–adrenal axis. Cholinergic underactivity appears crucial, explaining the propensity of drugs with anticholinergic properties to precipitate or contribute to delirium. Dopamine excess is also important, perhaps because of its regulatory action on cholinergic pathways. Inflammatory activity occurs with raised levels of a range of cytokines impairing cerebral function through disruption of neurotransmitter pathways and other mechanisms. Elevated peripheral pro-inflammatory cytokines can induce apathy. This is a normal response to illness ('sickness behaviour'), and delirium may in part reflect an exaggerated form of this process. Sustained hyperactivity of the hypothalamic–pituitary–adrenal axis (as a result of illness-related stress combined with ageing-related impaired cortisol regulation), with resulting hypercortisolaemia, may be important.

Structural factors

Visuospatial neglect, as is common in right cerebral hemisphere strokes, is due to disease in the right parietal lobe or the right inferior frontal lobe. Such patients neglect their left sides, and may read only the right-hand pages of a newspaper or eat only the right-hand portions of a meal. Attention is also selective, because the brain cannot take in everything it senses, and these parts of the right cerebral hemisphere are fundamental to selection and sustaining attention. Without these, vigilance falls. It is now apparent from research that these areas of the brain are also affected in delirium regardless of cause, as though parietal molecules have been thrown in the air like jigsaw pieces; when delirium settles, the pieces do not fall back fully into place, producing some permanent damage.

List some treatment principles in delirium

Non-pharmacological prevention or management of predisposing factors is summarised in Table 2.108.

Do you envisage any potential problems of drug treatment for delirium?

Potential problems include:

- Treating without searching for causes
- Not tailoring treatment to age / weight / degree of agitation

Table 2.108 Predisposing factors for delirium and their management

Predisposing factor (minimal provocation is all that is needed in vulnerable people with significant comorbidity)	Management
Cognitive impairment (dementia is a very common precursor) or disorientation	Provide appropriate lighting and clear signage A clock and calendar should be easily visible Reorientate the person by explaining where they are, who they are, and what your role is Introduce cognitively stimulating activities (for example, reminiscence) Facilitate regular visits from family and friends Reassure of safety and reality (do not collude with perceptual disturbances!)
Dehydration or constipation	Encourage the person to drink Consider subcutaneous or intravenous fluids if necessary
Hypoxia	Assess for and optimisation of oxygen saturation if necessary
Immobility or limited mobility	Encourage the person to mobilise soon after surgery, walk (provide walking aids if needed – these should be accessible at all times) or carry out active range-of-motion exercises Avoid bedrails – which convert delirium into delirium with a hip fracture!
Infection	Look for and treat infection Avoid unnecessary catheterisation
Multiple medications	Carry out a medication review for people taking multiple drugs
Pain	Assess for pain
Poor nutrition	Ensure optimum nutrition Ensure appropriate fitting dentures if used
Sensory impairment	Resolve any reversible cause of the impairment (such as impacted ear wax) Ensure working hearing and visual aids are available to and used by people who need them
Sleep disturbance	Avoid nursing or medical procedures during sleeping hours, if possible Schedule medication rounds to avoid disturbing sleep Reduce noise to a minimum during sleep periods

Table 2.109 Drugs for emergency sedation in confusion

Drug	Indications	When not to use	Side effects	Administration
Haloperidol	Emergency sedation	Withdrawal Anticholinergic toxicity Liver failure Dementia with Lewy bodies	Extrapyramidal Anticholinergic Hypotensive Prolonged QTc (torsades de pointes)	p.o. peak effect 4–6 hours 0.5–1 mg twice daily and as required i.m. peak effect 20–40 minutes 0.5–1 mg, repeated if needed at 30–60 minutes Maximum 5 mg in 24 hours
Lorazepam	Emergency sedation Alcohol withdrawal Parkinson's disease (to limit extrapyramidal effects of haloperidol)	Respiratory depression	Respiratory depression Paradoxical excitement	p.o. 0.5–1 mg 4-hourly as required i.v. (emergency) 0.5 mg Maximum 2 mg in 24 hours
Atypical antipsychotics Risperidone (R) Olanzepine (O) Quetiapine (Q)	Longer–term sedation O > Q > R but potency R > O > Q	Some evidence of increased cerebrovascular risk in dementia (perhaps also so for haloperidol)	Fewer interactions and fewer extrapyramidal side effects (safety Q > O > R) than haloperidol	Starting doses R 0.5 mg twice daily Q 25–50 mg once daily O 2.5–5 mg once daily
Valproate	Background cognitive impairment (sometimes useful if 'hyperactive')			

i.m., intramuscularly; i.v., intravenously, p.o., orally.

- Not increasing the scheduled dose if the patient requires a large number of extra doses
- Overusing psychotropics or benzodiazepines
- Starting treatment too late
- A poisonous pot pourri.

Judicious use (if at all) of psychotropic drugs is the aim.

When necessary, what drug choices are there?

These are listed in Table 2.109.

CASE 2.44 MILD COGNITIVE IMPAIRMENT AND DEMENTIA

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Elizabeth Russell, aged 82 years
> Thank you for seeing this lady who has become progressively confused and forgetful over the past year with an MMSE now of around 22/30. She lives alone and her past medical history includes a stroke 3 years ago for which she takes aspirin and simvastatin. Her blood pressure is well controlled. Her daughter is concerned that her mother is developing Alzheimer's disease.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Elizabeth Russell is an 82-year-old retired schoolmistress who has been increasingly confused and forgetful over the past year. Her daughter, who lives nearby, accompanies her. She reports that her mother has been increasingly frail since her stroke 3 years ago, but she has been managing alone with the aid of her daughter and son-in-law, having made a good physical recovery. She has had difficulties remembering days and months for a long time, but now worryingly has left the gas cooker switched on by mistake on at least two occasions. More rapid deterioration in short-term memory has been apparent in the last 6 months. Mrs Russell walks with a stick, and has a tendency to lean backwards with short, shuffling steps. There is no history of hallucinations. She has a history of hypertension. She takes aspirin, simvastatin and a sedative at night. She has never smoked and does not take alcohol. She herself does not believe there to be any cause for concern. Mrs Russell's daughter is concerned that her mother might have Alzheimer's disease.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Recognise that the patient may have dementia.** Dementia is a clinical syndrome characterised by a cluster of symptoms and signs manifested by difficulties in memory, disturbances in language, psychological and psychiatric changes, and impairments in activities of daily living. There are many definitions of dementia, but those based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria are standard (Box 2.103).

Folstein's mini-mental state examination (MMSE; Fig. 3.28), of which there are numerous versions, is the most widely used measure of cognitive function. A score of < 23/30 usually indicates cognitive impairment and an MMSE of 22 with 0–1/3 on recall outside the setting of delirium is likely to represent dementia, although no cognitive test alone should be used to diagnose dementia, and the history of the condition is vital. Asking a patient to draw a clock face and set the hands to 11.10 is a useful addition. More specialist neuropsychological testing is useful in borderline or difficult cases, and mild cognitive impairment or early dementia is possible with a 'normal' MMSE, especially in those with pre-morbid high-level cognition; the MMSE, notably, may not detect vascular dementia where memory may be preserved until disease is advanced. Other neuropsychological assessment measures used include the Cambridge Cognitive Examination (CAMCOG), the Addenbrooke's Cognitive Examination (ACE) and the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog).

■ **Consider the possible causes of dementia.** The features of dementia depend, crucially, on the lobes involved. The three common dementias, Alzheimer's dementia, vascular dementia and dementia with Lewy bodies (DLB), tend to cause global cognitive impairment, but, for example, Alzheimer's pathology tends to progress from 'back to front', starting in the hippocampus (medial temporal lobe) and progressing forwards, so that memory impairment occurs early and behavioural disturbance (frontal lobe driven) occurs late, in contrast to vascular dementia and the rarer frontotemporal lobe dementias which cause rapid behavioural change. As dementia progressively involves all parts of the brain recognisable features of other diseases may appear such as Parkinsonian features as the extrapyramidal system degenerates; in such a case, the benefits of dopaminergic drugs are almost certainly outweighed by the risk of worsening confusion and postural instability.

Box 2.103 **Definition of dementia**

1. *Memory impairment* (problems with learning new information often precede problems with recall of previously learned information).
2. At least one of another cognitive disturbance:
   - *Aphasia* (*language* disturbance)
   - *Apraxia* (problems with motor activities despite intact motor function)
   - *Agnosia* (problems recognising or identifying objects despite intact sensory function)
   - Disturbance in *executive functioning* (planning, organising, sequencing, abstracting, initiation, judgement, self-evaluation or insight – people think they do better at tasks than they really do).
3. The deficits in 1 and 2 *significantly impair social or occupational functioning* and are a significant decline from before (these include psychological and behavioural disturbances).
4. The deficits are not part of delirium or better accounted for by another disorder, e.g. depression.

   Problems reflect location. Symptoms reflect the area of brain affected (Fig. 2.14):
   - Memory loss arises from medial temporal lobe disease
   - Visuospatial problems, apraxias and agnosias, and language problems arise from parietal and temporoparietal disease
   - Executive dysfunction and apathy arise from frontal lobe disease or loss of connectivity with the frontal lobes.

A wider view

However, one might also take the view that dementia, at its core, means irreversible progressive brain dysfunction resulting from progressive brain pathology and thus any combination of features of a brain at fault may be manifest. This is especially relevant to the subcortical dementias where there is relative preservation of cortical function but significant loss of neurological function, notably gait disturbance, resulting from subcortical pathology, especially early in disease. One might also debate the distinction between an ageing brain and dementia. The population is ageing and allied to this is the prevalence of dementia. It would seem that the ageing population is developing a disease associated with the risk factors of life when in former generations other diseases (e.g. infection, cardiac) claimed more lives at an earlier stage. One might even debate whether or not, if better preventive strategies were available, the 'epidemic' of dementia might give way to other 'epidemics' of ageing body organs and tissues such as rising cancer rates in the very old.

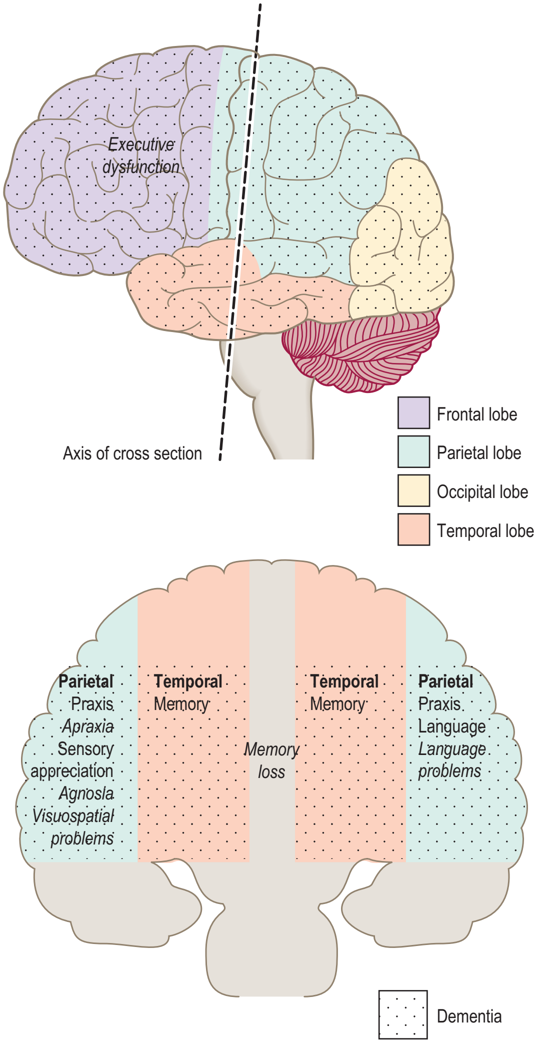


Figure 2.14 Cortical dementia

■ **Exclude reversible causes of cognitive decline.** This requires investigation, but treatable causes of cognitive decline (the term reversible dementia is a misnomer since dementia is by definition irreversible) include:

- The causes of delirium or acute confusion (Case 2.43 – Delirium)
- A range of 'subacute' encephalopathies (Case 2.43 – Delirium)
- A range of causes of insidious confusion that are not one of the common dementias (Box 2.104).

Furthermore, dementia is a 'vulnerable brain' risk factor that lowers the threshold for the occurrence of delirium, and delirium of any cause may induce irreversible damage to the brain, notably the parietal lobes, perpetuating inattentive problems and dementia.

Box 2.104 **Causes of chronic confusion that are not one of the common dementias**

These are important because they may be reversible (i.e. not dementia). There may be atypical features, such as rapid rate of onset or progression, or younger age of presentation. Causes include:

- Vitamin deficiency (B12, folate or B1)
- Hypothyroidism
- Subdural haematoma
- Tumours
- Human immunodeficiency virus infection (dementia or opportunistic infection)
- Neurosyphilis
- Prion disease/transmissible spongiform encephalopathy
- Normal-pressure hydrocephalus
- Depression and psychosis
- Drugs, alcohol and poisons.

Additionally, the range of subacute encephalopathies (Case 2.43 – Delirium) should be considered, as should rapidly progressive dementias such as frontotemporal degeneration.

Patient perspective

Insight into the safety issues appears to be blunted.

Past medical history

Hypertension and the previous stroke suggest that vascular dementia is possible. It is important to elicit any previous history of depression, as this can mimic dementia.

Drug and allergy history

Any drugs that can promote confusion such as sedatives can push patients more quickly down the slippery slope of cognitive decline. One should always be alert to the combination of selective serotonin reuptake inhibitors and tramadol, the latter itself serotonergic, and the combination contraindicated.

Family history

Dementia is very rarely familial, e.g. Huntington's disease.

Social history

Patients and their relatives often mistake early signs of dementia for normal ageing, but the expected cognitive changes in normal ageing, such as slower information processing, generally do not impede independent function. Dementia often comes to light only when behaviour or function is impeded to a disabling extent and there are fears from relatives for safety. Behavioural problems in dementia tend to occur late, and include verbal aggression/threats/mood swings, physical aggression/agitation, restlessness, wandering and apathy/withdrawal. Assessment of daily function is important in diagnosis, assessing response to treatment and planning future provision of care. Activities of daily living assessed include basic ones such as eating unaided, toileting, washing and grooming, dressing and walking, and more instrumental complex tasks such as cooking, shopping, housekeeping, self-medication, handling finances and driving.

SUMMARY BOX – ASSESSMENT AND PLAN

- The risk factors and upright shuffling gait suggest vascular dementia is the most likely dementia.
- Investigations ('dementia screen') should include full blood count, urea, electrolytes and creatinine, liver function tests, calcium, glucose, B12 and folate, thyroid function tests, urinalysis and neuroimaging (evidence of small-vessel disease, exclusion of hydrocephalus and subdural haematoma).
- Testing for neurosyphilis (cerebrospinal fluid for active disease) is occasionally indicated.
- Old age psychiatrists and clinical psychologists have an important role in the diagnosis, treatment, support and monitoring of patients with dementia, as does interception by the multidisciplinary team, e.g. occupational therapist.
- Cognitive enhancer therapy may be indicated if Alzheimer's dementia seems likely after more detailed assessment.
- Knowing the background level of physical agility and cognitive ability will aid explanation to the patient and family of what is likely to be achieved; this patient would not be expected to be leaping like a gazelle on the African plains following treatment.

Discussion

What is the prevalence of dementia?

Up to 20% of people over 80 years have some form of dementia, and prevalence almost doubles every 5 years from age 60 to 94.

What are the common types of dementia?

Common causes of dementia are:

- Alzheimer's disease
- Vascular dementia
- Mixed dementia (Alzheimer's dementia and vascular dementia)
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia.

Dementia may also be classified by location as well as by cause:

- Cortical dementia (e.g. Alzheimer's disease, vascular dementia, DLB, frontotemporal dementia)
- Subcortical dementia (e.g. subcortical vascular dementia, and Parkinsonian syndromes – e.g. progressive supranuclear palsy, Huntington's disease)
- Mixed location.

Why is it important to determine the cause of dementia?

Whilst different types of dementia have much in common, they tend to have different clinical courses, and can respond differently to treatment. For example, the symptoms of Alzheimer's disease can be modified with cholinesterase inhibitors, people with DLB who take antipsychotic drugs may have adverse effects, and the identification of vascular disease means that comorbidities can be treated which may delay progression of disease.

What do you know about vascular dementia?

Vascular dementia is cited as the second commonest dementia overall, but may be the commonest in people aged > 85 years (Table 2.110).

What do you know about subcortical vascular dementia?

This is explained in Case 5.50 ('Off legs').

What do you know about Alzheimer's dementia?

Alzheimer's dementia is the commonest dementia. Onset is gradual with continuing decline. There is no universally accepted set of diagnostic criteria for Alzheimer's dementia but features of Alzheimer's dementia are outlined in Box 2.105.

The relation between normal ageing and Alzheimer's dementia

Cognitive dysfunction is observable several years before a clinical diagnosis of Alzheimer's dementia. This dysfunction is not qualitatively different from that seen in normal ageing, suggesting considerable overlap in cognitive performance between normal ageing and this stable phase of preclinical dementia. Global cognitive deterioration, affecting memory and other aspects of cognition (e.g. language, visuospatial skills, attention, perceptual speed), is almost always a presenting symptom. The gradual onset of memory loss means that it may be misattributed to normal ageing and often recognised as due to Alzheimer's dementia in retrospect.

The pathology of Alzheimer's dementia

Alzheimer's dementia is a neurodegenerative condition macroscopically characterised by loss of neurons and synapses (atrophy) in the cerebral cortex (temporal lobe, parietal lobe, parts of the frontal cortex, cingulate gyrus) and certain subcortical regions. Alzheimer's dementia tends to start in the hippocampus. Histopathologically amyloid-β (Aβ) plaques and neurofibrillary tangles containing the protein tau (which normally acts to stabilise microtubules in the cytoskeleton) and ubiquitin characterise Alzheimer's dementia:

- Aβ plaques are dense, mostly insoluble extracellular protein that reflect failure to dispose of Aβ. Many researchers ('bap'tists) regard Alzheimer's dementia as a problem predominantly of Aβ plaques. Aβ is a short peptide that is a proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but is thought to be involved in neuronal development. Presenilins are part of an enzyme complex involved in APP processing and breakdown. Although Aβ is usually soluble, it undergoes a conformational change at

Table 2.110 Vascular dementia (VaD)

Pathology		Morphological types	Clinical features
Classic multi-infarct dementia and post-stroke dementia (classic multi-infarct pattern less common than formerly thought, whilst post-stroke dementia increasingly appreciated)	Infarcts in territories of large cerebral arteries, or small-vessel disease	Cortical dementia Infarcts predominantly cortical	Memory loss not always prominent Executive dysfunction pronounced
Microangiopathic / small-vessel disease (very much more common than formerly thought)	Arteriosclerosis or diffuse multiple lacunar infarcts in cortex, subcortical deep white matter, basal ganglia or brainstem Due to hypertensive microangiopathy or cerebral microembolism	Strategic infarct dementia Infarcts small but in strategically important regions producing disproportionately large clinical effects; the commonest problem is memory loss due to infarcts anywhere along the hippocampus – mamillary bodies – mammillo-thalamic tracts – thalamus – cingulate gyrus – entorhinal cortex chain	Heterogeneous, depending on location
		Subcortical VaD Arteriosclerosis and infarcts in deep white matter of basal ganglia, thalamus, cerebellum or brainstem with relative preservation of cortex	See Case 5.50

Less common types of VaD include:
- Multiple small infarcts in border zone of anterior and middle cerebral arteries (hypoperfusion resulting from carotid stenosis or cerebral embolism) producing granular cortical atrophy
- Cerebral vasculitis, often producing cortical dementia (but more commonly strokes, seizures or rapid encephalopathy)
- Post-ischaemic encephalopathies following cardiac arrest or hypotension in critical illness, producing cortical laminar necrosis, multiple post-ischaemic lesions or hippocampal sclerosis
- Cerebral haemorrhages from various causes (e.g. cerebral amyloid angiopathy very similar to CADASIL but older group)

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Box 2.105 **Alzheimer's dementia (AD)**

AD is characterised by cognitive dysfunction and predominantly affects the medial temporal and temporoparietal cortex, arising in the hippocampus, such that memory loss is a key feature. Patients typically have difficulty remembering day-to-day events, are unable to keep track of the day or date, and may misplace possessions.

Language or linguistic problems may develop when perisylvian temporoparietal structures are involved leading to word errors (paraphasias), comprehension problems and loss of literary skills in reading and writing (alexia and agraphia).

Visuospatial impairment may result in difficulty with tasks such as dressing, arranging objects, climbing stairs or finding the way, and driving may become unsafe because of loss of visuospatial awareness; in later stages failure of recognition occurs, which may include familiar faces, including family and even personal reflection in a mirror.

Despite these severe cognitive deficits, social façade is usually well preserved. The degree of insight may reflect the degree of memory loss. Neurological signs are generally absent though neuropsychological assessment reveals dense amnesia with varying combinations of visuospatial and constructional impairment and language problems.

Proposed diagnostic criteria for AD (Dubois B, Feldman HH, Jacova C et al) are:

Core criteria

A Early significant episodic memory impairment, including:
- Gradual and progressive change in memory function over > 6 months
- Objective evidence of significantly impaired episodic memory on testing
- Episodic memory impairment, isolated or associated with other cognitive changes at AD onset

Supportive criteria

B Medial temporal lobe atrophy on magnetic resonance imaging

C Abnormal cerebrospinal fluid biomarker: ↓ amyloid-β peptide 42, ↑ total tau, ↑ phospho-tau

D Specific pattern on functional neuroimaging with positron emission tomography

(not single photon emission computed tomography)

E Proven AD autosomal dominant mutation in the immediate family.

Probable AD requires A plus one or more supportive features B–E. Definite AD requires clinical features and neuropathological confirmation *or* the presence of a deterministic genetic mutation.

high concentrations to form a β-sheet-rich tertiary structure that aggregates to form amyloid fibrils that deposit outside neurons in dense Aβ plaques.

- Neurofibrillary tangles are insoluble twisted fibres that build up inside neurons and reflect failure to dispose of intracellular proteins including tau. Some researchers ('tau'-ists) still regard Alzheimer's dementia as predominantly a tauopathy. Altered phosphorylation and aggregation of tau leads to impaired axonal transport, synaptic loss and ultimately neuronal death, and also to neurotransmitter deficits, particularly in the basal forebrain cholinergic system. Tau pathology (neurofibrillary tangles) and synaptic loss correlate better with the degree of dementia than Aβ plaque burden.

The pathogenesis of many neurodegenerative disorders is associated with accumulation of protein deposits in brain parenchyma. A normal soluble cellular protein is converted into an abnormal insoluble toxic aggregated protein rich in β sheets, as in Aβ in Alzheimer's dementia. Many neurodegenerative disorders are associated with amyloid accumulation and many with trinucleotide CAG repeat sequences, which may cause protein aggregation. Research into treatments that inhibit or break down insoluble protein aggregates is ongoing.

The genetic basis of Alzheimer's dementia

Apolipoprotein E (ApoE) is a cholesterol transporter lipoprotein made in the liver with three isomers. The ApoE4 allele in its heterozygous and homozygous form is associated with an increased risk of Alzheimer's dementia, in which there is failure of elimination of Aβ. In familial Alzheimer's dementia (around 0.5–1%) mutations in genes for presenilin (PS1 and PS2 on chromosomes 14 and 1) or APP (on chromosome 1) lead to overproduction of Aβ. Research continues to identify other potential susceptibility genes, many of which may influence Aβ metabolism.

The mechanism of disease production in Alzheimer's dementia and how this may be linked with vascular disease

The oldest hypothesis is the 'cholinergic hypothesis', regarding Alzheimer's dementia as a deficiency primarily in acetylcholine production. But reduced levels of neurotransmitters including acetylcholine, serotonin and norepinephrine (noradrenaline), and elevated glutamate levels, are more likely to be induced by the disease than its cause. Some researchers still believe that tau is a primary causative factor, grounded in the observation that deposition of Aβ plaques does not correlate as well as tau with neuron loss. But the Aβ hypothesis is perhaps more compelling mechanistically and may eloquently explain the overlap of Alzheimer's dementia and vascular dementia. Three main mechanisms are involved in eliminating Aβ from the brain, each of which can fail with age:

- Aβ is degraded by amyloid proteases including neprilysin and insulin-degrading enzyme within brain parenchyma.
- Aβ is absorbed into the blood by receptor mechanisms including low-density lipoprotein receptor-related protein-1.
- Aβ is eliminated via perivascular lymphatic drainage mechanisms. In healthy young people, interstitial fluid and nutrients enter the brain through the tightly controlled blood–brain barrier whilst fluid and soluble waste metabolites exit the brain via narrow extracellular spaces between neurons to enter bulk flow pathways along the basement membranes coating the walls of capillaries and the smooth muscle cells of arteries. There is theoretical evidence from mathematical models that contrary or reflection waves that follow each arterial pulse wave provide the motive force for drainage along these pathways in the opposite direction to that of arterial flow (i.e. out of the brain) and changes in the artery wall as the vessel expands and recoils may provide valve-like impedance to fluid and waste metabolites being driven back into the brain by the much stronger pulse wave.

Perivascular drainage failure is common with age as drainage is dependent upon expansile arteries. Arteriosclerosis, the process of generalised fibrous scarring (as opposed to focal atherosclerosis), often due to hypertension, slows perivascular drainage. This results in:

- Deposition of insoluble Aβ within artery walls and an increase in cerebral amyloid angiopathy (which can cause recurrent intracerebal haemorrhages)
- Progressive failure of elimination of Aβ from the brain
- Retention of soluble Aβ, which may be particularly likely to cause cognitive disturbance since high levels of soluble Aβ appear to be toxic to neurons.

What do you know about mixed dementia?

Alzheimer's dementia and vascular dementia thus increasingly form a spectrum of dementia (Fig. 2.15). Alzheimer's pathology with plaques is common, but not necessarily associated with dementia. However, when arteriosclerosis triggers failure of perivascular drainage this leads to cerebral amyloid angiopathy and accumulation of soluble as well as insoluble Aβ, which appears to trigger dementia. At the other end of the spectrum is pure vascular dementia due to focal atherosclerosis or thromboembolism.

It is increasingly clear that the contemporary view of Alzheimer's dementia as 'presenile' dementia and vascular dementia as 'senile' dementia with different age of onset peaks are extremes of a spectrum in which Alzhemier's pathological changes result in dementia when cerebral perfusion is impaired. Nearly all risk factors for Alzheimer's dementia have a vascular component and regional blood to memory parts of the brain is impaired in Alzheimer's dementia, increasingly identifiable with neuroimaging; indeed, microvascular changes are apparent before degenerative changes and clinically apparent disease.

Thus, hypertension and microvascular disease, often with microscopic lacunar damage, which often starts in subcortical areas, provide a rational mechanistic basis for subcortical as well as cortical vascular or mixed dementias.

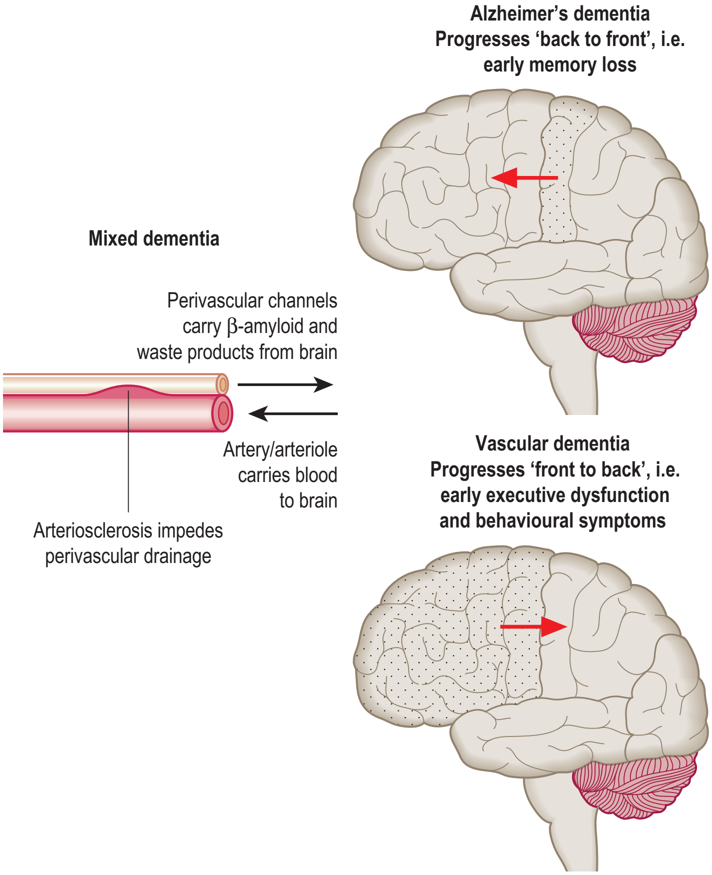

Alzheimer's dementia
Progresses 'back to front', i.e. early memory loss
Mixed dementia
Perivascular channels carry β-amyloid and waste products from brain
Artery/arteriole carries blood to brain
Arteriosclerosis impedes perivascular drainage
Vascular dementia
Progresses 'front to back', i.e. early executive dysfunction and behavioural symptoms

Figure 2.15 Alzheimer's dementia, vascular dementia and mixed dementia. Alzheimer's dementia progresses 'back to front', i.e. with early memory loss. Vascular dementia may progress 'front to back', i.e. with early executive dysfunction and behavioural symptoms. Mixed dementia has either cortical or subcortical dominance.

Differentiating Alzheimer's dementia and vascular dementia clinically can be difficult, and the potential overlap of pathologies may be one reason for this. Numerous sets of criteria are commonly used to diagnose Alzheimer's dementia, and many more exist for vascular dementia in clinical and research settings. Brain-imaging evidence of vascular disease is required, though the nature and extent to meet a diagnosis of vascular dementia have not been clearly defined. Vascular dementia is strongly supported by neurological clinical features, and the presence of a temporal relationship between brain lesions on imaging and dementia. Abrupt-onset or stepwise deterioration following a stroke is typical of post-stroke vascular dementia, whereas Alzheimer's dementia produces gradual onset and deterioration, such as progressive memory loss. The increasingly appreciated notion is of mixed Alzheimer's dementia and vascular dementia, with a spectrum between pure Alzheimer's dementia and pure vascular dementia, in which mixed dementia occupies the biggest proportion. Differentiating between Alzheimer's dementia and vascular dementia is difficult enough, without the added difficulty of diagnosing mixed dementia, a condition for which there are no clear diagnostic criteria. However, the notion of mixed dementia has gained ground as it is now apparent that many patients have Alzheimer's dementia pathology that is a quiescent or latent explosive until cerebrovascular disease arises and acts as the trigger to ignite it.

What do you know about DLB?

DLB is probably the third commonest dementia after Alzheimer's dementia and vascular dementia (and the mixed spectrum) and is under-recognised. It is 'suggested' if one of the three features in Box 2.106 is present and 'probable' if two are present.

Parkinson's disease dementia versus DLB

Up to 90% of Parkinson's disease patients develop cognitive impairment, and 20–40% frank dementia, associated with cholinergic deficiency. Parkinson's disease dementia is generally defined as dementia fulfilling dementia criteria (Box 2.103) in the setting of Parkinson's disease motor symptoms of at least a year's duration. DLB arises earlier or without Parkinson's disease. They are both synucleinopathies (α-synuclein is the protein that aggregates to form Lewy bodies) and distinguishable from other dementias by the features in Box 2.106, early sparing of short-term memory, a tendency to autonomic dysfunction and falls and sensitivity to neuroleptics, which should be

Box 2.106 **Dementia with Lewy bodies (DLB)**

This should be suspected when any of the following are present, particularly if exacerbated by antipsychotics, which are absolutely contraindicated in DLB.

1. Fluctuating cognition

This is with marked variation in attention and alertness. Patients might typically be admitted to hospital with recurrent 'urinary tract infections and confusion'.

2. Recurrent visual hallucinations, often of people or animals

Typical hallucinations are of small children, cats and dogs, and sometimes exotic wildlife such as leopards, lions and elephants. In the author's experience, monkeys are inexplicably common. Sometimes there may be richly detailed panoramic visions of landscapes, rivers or armies of people. Typically hallucinations come at certain times of the day then dissipate, and may build over time. For example, a woman living alone might experience strangers coming to the house for tea in the late afternoon, who may subsequently visit each day and become more demanding, expecting meals and then settling in to watch television, ultimately staying very late. Her family might visit in the morning to find cups of tea and uneaten meals on the table and the television still on. Hallucinations tend to be more of a nuisance to patients than frightening. They may settle in hospital, where the distractions of light and noise suppress the twilight visits of children or ghostly shadows that creep through the curtains at home (sun-downing symptoms). These often colourful, detailed hallucinations are quite unlike the disturbance of acute confusion, which tends to be a general agitation without such formed experiences and which often worsens in hospital.

3. Parkinsonian features

Lewy bodies may be restricted to the extrapyramidal system when they are associated with pure Parkinson's disease, scattered through the cortices to cause DLB or present in both areas, often causing dementia in the later stages of Parkinson's disease. Lewy bodies thus ascend the subcortical–cortical ladder in Parkinson's disease and descend it in DLB.

avoided. Rivastigmine may be used in mild to moderate Parkinson's disease dementia and DLB.

Nobody knows why these characteristic hallucinations occur in DLB. Some food for thought is that Parkinson's disease starts in the midbrain olfactory bulb. This, in fish, was the highest part of the brain. Sense of smell remains a highest sense in many animals, and sharks can scent droplets of blood from miles away. Also in the midbrain are other primitive senses such as a primitive visual pathway that is sometimes recruited unconsciously by people who are blind in the rare condition known as blindsight. So in DLB we have a condition in which the converse of Parkinson's disease occurs, and the cortex is diseased with relative preservation of the midbrain, allowing, perhaps, the midbrain to exert a little more primitive control of experiences (which may include awareness of threats and nurturing roles) and it may be that in DLB, unlike all other dementias, there is a relatively unique sparing of the midbrain in conjunction with a unique pattern of cortical disease. Of course patients with Parkinson's disease dementia may also develop hallucinations, as they may on Parkinson's disease medications, with dopaminergic effects, but the hallucinations in Parkinson's disease are not always the same as those in DLB. There is also the fact that DLB tends to be a rather posterior disease with occipital involvement.

Charles Bonnet syndrome

This is a syndrome of new visual hallucinations (that may superficially mimic DLB) in the absence of delirium, dementia or neuropsychiatric disorder. Mean age of onset is 57 years. Hallucinations are often complex, and may be of animals or people or landscapes, often with distorted or magical shapes such as small people wearing bright clothes and silly hats. Patients usually have insight and may be visually impaired with age-related macular degeneration or cataracts. It seems that visual deprivation may lead to compensation by the brain to find patterns to explain the external world based on previous visual experiences, an extension of the vivid imagination that may lead us to see shapes in clouds or faces in flames, and is in a sense similar to phantom limbs in amputees or tinnitus in sensorineural hearing loss in that the cortex still searches for meaning with absent peripheral sensation. The differential diagnosis of course includes seizures, delirium and dementia, not least DLB, but in the latter cognitive impairment exists with hallucinations generally unleashed by sun-downing, whereas in Charles Bonnet syndrome they appear in broad daylight. Charles Bonnet syndrome is perhaps more accurately a disorder of illusory than hallucinatory misperception, although there may be a predisposition to dementia.

What do you know about frontotemporal dementia?

Frontotemporal degeneration is associated with severe atrophy of the frontal lobes and anterior temporal lobes. The syndrome resulting depends on the preferential site of atrophy – bifrontal in frontotemporal dementia, temporal in semantic dementia and left frontotemporal in progressive non-fluent aphasia. They are usually tauopathies and relatively rare, although frontotemporal dementia is perhaps the second commonest cause of 'presenile' dementia after Alzheimer's dementia. Progression is often relatively fast. Frontotemporal dementia may be of classical type, frontotemporal dementia-1 or a primary progressive aphasia.

Frontotemporal dementia-1

Early features are change in personality, and social and behavioural change. There is rapid inability to manage personal affairs such as work and finance. Disinhibition and overactivity or inertia with lack of motivation may predominate and as disease progresses overactivity may give way to inertia but not vice versa. There is loss of insight and emotional shallowness develops. Stereotyped behaviours such as repetitive actions and complex rituals such as cramming food into the mouth may occur. Neuropsychological assessment reveals frontal lobe deficits such as severe difficulties in planning and strategic skills, concrete and perseverative responses, impulsive behaviour and apathy. Visuospatial function is preserved.

Semantic dementia

Patients lose the meaning of words and objects. Speech is fluent and effortless, but empty and filled with semantic (verbal) paraphasias or errors with a progressively limited repertoire. Visuospatial function is preserved.

Progressive non-fluent aphasia

The predominant defect is a circumscribed language disorder and, with progression, mutism.

What do you know about prion diseases or transmissible spongiform encephalopathies?

The term prion disease is often used interchangeably with Creutzfeldt–Jakob disease (CJD), but CJD is but one form of prion disease or transmissible spongiform encephalopathy (TSE), albeit the most common. TSEs are diseases caused by proteinaceous infectious agents (which are not organisms) called prions; these are proteins derived from simple genes on chromosome 20 (in the case of CJD), coding for the prion protein (PrP). PrP is ubiquitous. We all have PrP, and its natural function is uncertain. When PrP is mutated it causes disease by aggregating into amyloid-like plaques. How prions actually cause disease is unclear, even to experts at the CJD Surveillance Unit. At its most simplified, it appears that this normal brain protein, for some unknown reason in those affected, unfolds, and as it unfolds it loses its natural function, which leads to aberrant function and cell death. Even more curious is that this abnormal protein, if ending up in another organism, even from another species, may then induce that 'infected' organism's normal prions to begin unfolding, too. TSEs include:

- CJD prion diseases – sporadic (more than 85%) CJD; inherited (familial, autosomal dominant) CJD
- New variant CJD (nvCJD prion)
- 'Kuru' (acquired by ingestion of the kuru prion, notably in cannibalism)
- Other rare inherited prion diseases, e.g. Gerstmann–Sträussler–Scheinker syndrome (GSS prion), fatal familial insomnia (FFI prion).

Sporadic CJD

This is characterised by rapidly progressive dementia (often with memory loss, and some degree of passivity or loss of insight) and myoclonus, often with cerebellar ataxia, resulting from neuron loss in a spongiform (vacuolated) brain with gliosis. The illness causes rapid decline over months. The UK incidence is around 1 in 1–1.5 million/year, or 70–80 cases. Magnetic resonance imaging (MRI) may show cortical and basal ganglia inflammation, although appearances can vary. Most patients have periodic sharp complexes on electroencephalography (EEG), although only at a window in time. The cerebrospinal fluid (CSF) will reveal high levels of tau protein (a non-specific indicator of brain cell death) and elevated levels of 14 : 3 : 3 protein and S-100 protein. CJD is transmissible via exposure to CSF and neuronal tissue, although probably only by direct mucosal contact; for this reason great cautionary measures are taken at autopsy, although routine lumbar puncture should pose no risk. The laboratory handling CSF samples should be made aware of any patient with suspected CJD although universal precautions should have always been taken. Because the nefarious prion is not denatured by temperature all materials used should be appropriately disposed of and not recycled.

New variant CJD

The nvCJD or bovine spongiform encephalopathy (BSE) tends to affect a younger age group, and presents with early neuropsychiatric symptoms and ataxia. The EEG is not typical.

What is normal pressure hydrocephalus (NPH)?

CSF is produced by the choroid plexus and normally flows from the lateral ventricles, through the foramen of Monroe to the third ventricle, via the aqueduct of Sylvius to the fourth ventricle, and then via the foramina of Magendie and Luschka into the subarachnoid space where it is absorbed by the villi. In NPH there is no obstruction, the hydrocephalus communicating, and a CSF absorptive defect seems the most likely cause of CSF accumulation, the arachnoid villi seeming to take long tea breaks! This gives rise to the triad of:

1. Gait change (there is no classical pattern but gait apraxia or an ataxic, wide-based gait are the commonest problems; a magnet gait, being glued to the spot, postural instability and a tendency to fall backwards are also common and upper limb and mouth apraxia can occur)
2. Urinary incontinence (this is the result of frontal indifference, giving rise to frequency and urgency)
3. Dementia (this is a late sign, and usually mild to moderate; severe dementia is a bad prognostic sign unlikely to respond to shunting).

Psychological morbidity is high even without dementia – apathy, bradyphrenia, somnolence and asthenic emotional disorder. NPH can sometimes mimic Parkinson's disease – the frontal lobe connections to basal ganglia are involved in sequence learning.

Computed tomography (CT) scanning reveals ventricular dilatation out of proportion to sulcal enlargement because the problem is not atrophy. Frontal periventricular lucencies 'due to probable small vessel disease' are not a reason to dismiss possible NPH. MRI may reveal an absence of gross hippocampal atrophy or marked subcortical white matter changes, periventricular high signal on T2-weighted images, upward bowing of the corpus callosum, flattening of gyri against the inner table or increased aqueductal flow, all strongly correlated with a response to shunting. MRI may be important in confirming CT suspicions and in excluding non-communicating (obstructive) hydrocephalus – a colloid cyst, for example, may be difficult to see on CT but potentially lethal if it suddenly swings to obstruct flow (classically on fairground rides or with shifts in CSF pressure at lumbar puncture!).

Assessment for shunting can involve clinical tests such as walking tests pre- and post-therapeutic lumbar puncture, with physiotherapy assessment if gait disturbance is the most troublesome feature, reaction time tests such as pressing a mouse in response to auditory or visual stimulation and memory tests such as an MMSE if cognition is impaired. An improvement of 5% after CSF removal is often taken as a positive result. The best test might be if the patient or a spouse sees a difference.

Generally around 30 ml of CSF is an appropriate amount to take off initially. An alternative lumbar infusion test (in specialised centres) is positive if CSF plateau pressure is over 22 mmHg or if it does not plateau but keeps rising to over 40 mmHg. Fifty millilitres of CSF is then removed over 20 minutes and walking and reaction tests are repeated 2 weeks later.

NPH is a misnomer – there must be increased pressure at times, although when CSF is removed pressure is invariably normal and NPH might more accurately be called 'intermittently normal pressure hydrocephalus'.

If diagnosed and managed early with a shunt, NPH is fully reversible, and a standard management pathway if NPH is suspected on CT is MRI, therapeutic lumbar puncture and, if improvement is seen (sometimes early, sometimes after a week or two), referral to a neurosurgeon.

What investigations might be considered in dementia?

Investigations may be important to exclude reversible causes of cognitive decline, add evidence to a likely diagnosis or monitor progression.

Blood tests

Routine blood tests should include a full blood count, electrolytes, renal and liver function tests, calcium, glucose, thyroid function and a vitamin B12 level. Serology for syphilis and human immunodeficiency virus are sometimes considered. It is important to be alert to rarer, often rapidly progressive dementias and encephalopathies, some of which may be treatable.

Neuropsychological assessment

This should be considered a component to assessing dementia.

Neuroimaging

Neuroimaging offers exciting current and future advantages, as follows.

Structural imaging

MRI is much more helpful than CT.

- In Alzheimer's dementia there is classically symmetrical hippocampal and mesial temporal atrophy, explaining the predominant memory loss. There is often posterior cortical atrophy such that there is a large posterior–anterior atrophy gradient and the frontal lobes and pyramidal tracts are usually spared; some patients have predominantly posterior cortical atrophy, with predominant visuospatial disturbance.
- Vascular dementia often overlaps with Alzheimer's dementia. Classic multi-infarct dementia seems rare, despite its popularity, though dementia is well recognised following large-artery stroke syndromes. Strategic infarcts in critical areas may be detected but can be very small. Diffuse small-vessel disease detected on structural imaging appears to correlate well with vascular risk factors but less well with cognitive impairment. White matter lesions are more common in people with vascular dementia and Alzheimer's dementia but should be interpreted with caution as they may have other causes and may occur in apparently healthy people.
- DLB produces global volume loss that is non-specific. Other Parkinsonian neurodegenerative syndromes are also not usually diagnosable on structural imaging – corticobasbal degeneration produces non-specific non-regional volume loss; progressive supranuclear palsy often produces midbrain atrophy, however.
- In frontotemporal dementia there is severe asymmetric frontal and anterior temporal atrophy and this is easy to distinguish from Alzheimer's dementia on MRI. In semantic dementia there may be severe temporal atrophy that may be asymmetric. In primary non-fluent aphasia there is selective left frontotemporal atrophy.

A typical radiological sequence in dementia might include axial T2-weighted MRI and fluid-attenuated inversion–recovery imaging to assess ischaemic load, T1-weighted MRI and gradient echo to detect regional atrophy and diffusion-weighted imaging (DWI) to detect small haemorrhages.

Functional imaging

Positron emission tomography and single photon emission computed tomography can provide information about blood flow and metabolism with, for example, radiolabelled glucose.

- In Alzheimer's dementia functional imaging may show hypoperfusion to the temporal lobes and adjacent parietal structures, significantly before atrophy changes of become apparent on MRI.
- In vascular dementia changes may be heterogeneous and patchy. DWI and diffusion tensor imaging may provide information on 'connectivity' – it is increasingly realised, for example, that subcortical vascular dementia produces many of its symptoms as a result of loss of key connections to the cortex. Functional MRI may be used for task-dependent studies which analyse blood flow to certain areas of brain, but may also be used to assess resting state connectivity.
- In DLB changes tend to be more posterior than anterior.

- In frontotemporal dementia there is reduced cerebral blood flow in areas corresponding to changes, in semantic dementia reduced blood flow in the temporal and later frontal areas and in progressive non-fluent aphasia reduced blood flow in the left cerebral hemisphere.

MR spectroscopy may help differentiate some specific types of dementia, analysing brain metabolites, although findings often overlap. For example, decreased levels of *N*-acetyl aspartate reflect neuronal loss or dysfunction and increased levels of myo-inositol reflect glial cell disruption; these changes occur in Alzheimer's dementia, frontotemporal dementias and prion disease, amongst others. Intriguingly, these changes may occur in mild cognitive impairment and years before the clinical onset of Alzheimer's dementia raising the possibility of early diagnosis.

Pathology imaging

This is early in its evolution but is likely to develop. Amyloid, for example, contains iron, and imaging with Pittsburg compound B, for example, can detect amyloid plaques. There is now interest in techniques to detect soluble amyloid and tau.

Electroencephalography (EEG)

EEG may be a useful adjunct, especially if CJD or transient epileptic amnesia is suspected. EEG in Alzheimer's dementia shows non-specific slow waves, in vascular dementia there may be slow waves, in DLB there is often gross slowing and in frontotemporal dementia the EEG tends to be normal.

CSF analysis

CSF analysis is occasionally helpful, usually in assessing for reversible or rapidly progressive encephaolopathies or for CJD.

Genetic testing

Testing for known mutations (e.g. history of autosomal dominant dementia) may be offered in specialist centres.

Tissue biopsy

This is occasionally undertaken for some rare dementias

What treatment considerations are there in dementia?

The benefits of identifying early dementia

Cognitive impairments in the early stages of Alzheimer's disease may remain stable for several years. These correspond to the clinical concept of mild cognitive impairment, with subjective symptoms (predominantly of memory loss) and measurable cognitive deficits but without notable impairment in defined activities of everyday life. The stable phase of mild cognitive impairment lasts 2–5 years, in which semantic memory (the store of facts and general knowledge) and implicit memory (the non-conscious influence of past experience on subsequent performance) is also affected. People with amnestic mild cognitive impairment are up to 15 times more likely to develop dementia. Currently, stringent tests of episodic memory are the best neuropsychological predictors of subsequent conversion from mild cognitive impairment to Alzheimer's disease.

The potential downside of 'labelling' a person with a progressive and feared diagnosis at an early stage should be balanced against the advantages of excluding reversible conditions, instigating disease rate-limiting strategies, and opportunities to predict and plan care, notably at a stage when the patient is able to provide competent communications of her or his future wishes and thus engage in advance care planning. All of this emphasises the need for sensitive, expert and multidisciplinary approaches to making and communicating the diagnosis and ongoing care.

Treatments used in dementia

Non-drug interventions should be tried first, especially when symptoms are neither causing distress nor posing risk. Continuity of care is important, establishing good rapport with the patient and their carers. Programmes of care that involve both the patients and their families and are more intensive and modified to carers' needs may be the most successful.

Cognitive symptoms and cholinesterase inhibitors

Reduced cholinergic activity is associated with Alzheimer's and other forms of dementia. The acetylcholinesterase inhibitors (donepezil/Aricept, 5–10 mg; rivastigmine/Exelon, 6–12 mg; galantamine/Reminyl, 8–24 mg) have a moderate but worthwhile symptom-modifying effect in a substantial minority of patients with Alzheimer's disease and are generally well tolerated. They inhibit cholinesterase, which breaks down acetylcholine, raising the level of the acetylcholine. Memantine (10–20 mg) is a glutamatergic partial antagonist/*N*-methyl-D-aspartate receptor antagonist that some trials have found effective in people with more severe dementia, but it is not recommended by the National Institute for Health and Clinical Excellence (NICE). Galantamine has been specifically studied in Alzheimer's dementia with concomitant cerebrovascular disease and appears to confer benefits.

NICE supports use of the MMSE (with treatment between scores of 20 and 10 and 6-monthly checks, stopping if < 10, although remaining on the medication may soothe behavioural disturbance), but also the Addenbrooke's 100-point test battery to improve assessment. The MMSE may be less reliable in people with hearing or visual problems or without good English. The problem is that people with scores over 20 may derive significant benefit and a score of 27 or 28 may belie considerable global cognitive impairment, often compensated for if background intelligence is high, and unmasked only by behavioural psychology assessment. Acetylcholinesterase inhibitors are thus often used with scores above 20, not least by geriatricians.

Research is exploring immunotherapies and inhibitors of the secretase enzymes which cleave APP to produce Aβ.

Non-drug approaches are not effective in modifying memory loss, although memory-retraining techniques can offer support and improve well-being.

Secondary vascular prophylaxis makes sense where there is evidence on neuroimaging of cerebrovascular disease although evidence is not yet robust.

Non-cognitive (also known as the behavioural and psychological) symptoms

These include agitation, delusions or hallucinations. If a person with dementia develops distressing symptoms or challenging behaviour, assessment to identify modifiable factors (e.g. depression, drug side effects, pain, new environment) is important. Although antipsychotic drugs reduce agitation, they seem to have little specific benefit on psychosis (although they are still licensed for this), and there are concerns about the safety of both older (e.g. haloperidol) and second-generation (e.g. risperidone, olanzapine) antipsychotics in terms of stroke risk, mortality and worsening cognition. Trials with donepezil have shown conflicting results in its ability to improve behavioural problems. Rivastigmine may be beneficial in reducing behavioural problems in DLB. Other drugs may be effective, but evidence is patchy and drug treatment should be used with great caution, if at all. Mild agitation may be helped by lorazepam 0.5–4 mg, trazodone 50–300 mg, sodium valproate 250 mg to 1 g, carbamazepine 50–300 mg or cholinesterase inhibitors (particularly rivastigmine 1.5–6 mg in DLB). Severe agitation or the presence of psychosis may require quetiapine 25–200 mg, risperidone 0.5–2 mg, olanzapine 2.5–10 mg or aripiprazole 5–15 mg. Severe behavioural problems occasionally require haloperidol in small doses but this should be time limited. If depressive symptoms are present selective serotonin reuptake inhibitors such as citalopram 10–20 mg, or mirtazapine 15–45 mg, may be considered.

Therapeutic implications of the relationship between Alzheimer's dementia and vascular dementia

Cholinesterase inhibitors enhance levels of acetylcholine to compensate for loss of this transmitter in Alzheimer's dementia. However, levels of acetylcholine may have negative effects of perivascular drainage. The logical approaches for which there is evidence include preservation of artery elasticity with rigorous antihypertensive strategies (angiotensin-converting enzyme inhibitors significantly reduce dementia), statins, exercise and maintenance of cognitive activities (which may maintain favourable neurotransmitter profiles).

Driving

Surveys of drivers aged more than 80 with normal cognition consistently show prudent driving behaviours. Further, many patients continue to drive safely after dementia has been diagnosed, and withdrawal of their licence should not be undertaken lightly since stopping driving can limit social interaction and is an independent risk factor for entry to a care home. However, people with dementia eventually lose the ability to drive safely and at that point Driver and Vehicle Licensing Agency (DVLA) regulations demand that driving stops. The risk of crashes in patients with dementia is significantly increased but generally seems acceptably low for up to 3 years after onset, by which time most patients have already surrendered their licence.

The DVLA is legally responsible for deciding medical fitness to drive, but for several conditions, including dementia, doctors should advise patients of the possibility of stopping driving and take steps to ensure that the relevant statutory authorities are informed of breaches of regulations if there is concern about public safety. Any patient with dementia who is driving should be advised to inform the DVLA and their insurance company. If considered immediately unsafe by the doctor, the patient should be advised not to drive. If the patient fails to inform the DVLA, the advice should be reiterated, and then in writing, and if the patient still fails to notify then the doctor may disclose information to the DVLA, advising the patient of their intention to do so. The DVLA, informed by patient or notified by doctor, will request a medical report with or without an on-road assessment and make a decision to issue an annual licence or revoke it.

The DVLA accepts the difficulty assessing driving ability in dementia. Clinicians can perform various clinical, cognitive and behavioural tests, and activities of daily living tests, to complete a DVLA report, but evidence suggests that no cognitive test (e.g. MMSE, clock drawing or trails test) is robust enough to distinguish between patients with early Alzheimer's disease with capacity to drive safely and only assist in determining the need for further evaluation of driving.

The DVLA states that anyone holding a driving licence must, by law, inform the DVLA when given a diagnosis of any medical condition that might affect safe driving. Licences are normally valid until age 70, unless restricted for medical reasons. The DVLA requires confirmation at age 70 that no medical disability is present. All licence applications require a self-declaration of medical status by the applicant. The maximum licence period after age 70 is 3 years, subject to satisfactory completion of medical questions on the application. The DVLA must be notified as soon as Alzheimer's disease or another dementia is diagnosed. Drivers have an obligation to make such a declaration. The DVLA is aided in its decision on fitness to drive by medical reports. Patients with poor short-term memory, disorientation, and lack of insight and judgement are almost certainly not fit to drive (e.g. results in driving the wrong way round roundabouts, getting lost in familiar areas, miscalculating speed and distances). In early Alzheimer's disease, where sufficient skills are retained and disease progression is slow, a licence may be issued subject to annual review. A formal driving assessment may be necessary; the patient is assessed on a predetermined route in a vehicle with dual controls.

Can dementia be prevented?

Ageing involves two factors – programmed death and random damage.

Programmed mechanisms have genetic links, for example the *APOE4* genotype and a tendency to Alzheimer's dementia and *APOE2* and longevity. Cell senescence is linked with chromosome integrity. Chromosomes have non-sense, telomere sequences of DNA at their ends; these shorten with the number of cell replications and with age. Telomere shortening or damage is associated with senescence arrest (and essentially, the 'stuff of old age' such as osteoarthritis, atherosclerosis and skin fragility), apoptosis and attempts to repair; telomerases (which add DNA sequence repeats) prevent telomere shortening but at the price of increased mutation and susceptibility to cancer. Approximately 70% of genes are associated with repair rather than other functions, a reason why we share such genetic similarity to species as remote as bananas.

Random damage occurs in response to exogenous factors such as diet, infection and environmental toxins (essentially, the 'stuff of life') and, as common denominators, creation of oxygen free radicals, mitochondrial dysfunction (notably in dementia and cataracts) and telomere shortening. Protein and glucose, essential for life, produce protein glycosylation or advanced glycation end products (AGEPs) and these, along with oxygen species, are life's two notorious ageing substances. AGEPs, for example, produce browning of teeth, corneal staining and skin wrinkling and can associate with low-density lipoprotein–cholesterol to promote atherosclerosis, renal dysfunction and bone fragility, and are also linked with Alzheimer's disease. They are unavoidable, and irreversible.

Longevity elixirs, for which there is some evidence, include low-calorie diets and exercise. Low-energy diets with normal protein, fat and vitamins may postpone the disease of ageing, but at the price of a more miserable existence, growth reduction, decreased fertility and poor thermogenesis. Cardiovascular disease is associated with decreased physical activity at any age. Exercise improves blood pressure, insulin sensitivity, lipid profiles and even brainstem cell differentiation and learning, notably attention and reaction times. There is emerging evidence that 'thinking' affords us significant protection from dementia, and even where pathological changes of dementia are present clinical expression can be markedly tamed. Exercise and thinking appear to preserve telomere length, enhance growth factor expression and lower lipid peroxidase stress in the hippocampus, and increase brain capillary density, insulin-like growth factor-1 levels and antioxidant glutathione peroxidase levels. Evidence is accumulating that some interventions may delay the onset of dementia, which include:

- Keeping the brain active
- Eating healthily
- Being physically active
- Managing blood pressure, cholesterol, glucose and weight
- Participating in social activities
- Not smoking and drinking alcohol only in moderation
- Protecting the head from injury.

CASE 2.45 INCONTINENCE

Candidate information

Role

You are a doctor on the medical ward. Please read the following scenario. You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Isabella Lincoln, aged 62 years
>
> Mrs Lincoln is recovering from pneumonia on your ward. On your ward round, she mentions that she has been troubled by 'leakage of urine' for some years but that it has become more troublesome in the past few months. She mentioned it to the admitting doctor but nothing appears to have been done and she wonders if this could be assessed before she is discharged.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case. You are not required to examine the patient.

Patient information

Mrs Isabella Lincoln is a 62-year-old woman recovering in hospital from pneumonia. She has been troubled by urinary incontinence for years, and is now afraid to go out because of it. She finds her bladder will empty large volumes without provocation and she has to wear significant padding to prevent a 'flood'. She has no bowel symptoms. She is usually well, although her doctor commenced furosemide 20 mg some 10 years ago for ankle swelling around the time of the menopause, which she still takes. She has some vaginal irritation. She is a widow, and lives alone with two cats. She has plucked up the courage to ask the ward doctor if there are any treatments for incontinence.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Incontinence is a clinical diagnosis and a little knowledge about what to ask, investigation and treatment can make a large difference to a significant majority of patients.

■ **Explore symptoms of possible causes.** There are various types of urinary incontinence (Table 2.111).

An alternative way of categorising causes is as a *storage problem* (e.g. detrusor instability, stress incontinence, small bladder) or an *evacuation problem* (e.g. outflow obstruction, neuropathic bladder).

■ **Exclude aggravating factors.** Incontinence in older people is often stress, urge/overactive bladder or functional from immobility (e.g. arthritis, stroke, Parkinson's disease). It is often multifactorial with many factors precipitating:

- Altered bladder capacity, reduced tolerance and increased post-void volumes with age
- Pelvic floor muscles weaken with age
- Antidiuretic hormone diurnal variability decreases with age, with increasing need to get up at night
- Fluid retention is more likely, as in heart failure
- Those with chronic lung disease may have added cough-induced continence problems
- Drugs are common causes, e.g. diuretics, tricyclic antidepressants, opioid-induced constipation
- Bladder irritants, e.g. tea, caffeine, alcohol, acidic fruits, chocolate.

A common scenario is an elderly patient in a hospital or nursing home with an overactive bladder who cannot mobilise easily, may not be able to navigate a new environment and may have difficulty undressing appropriately on finding a toilet.

Patient perspective

Incontinence is a common clinical problem, and is underreported. It is more common in females, and more common in the elderly, although a number of studies (including one on college students in the USA) report that unstable bladder incontinence sometimes occurs in young healthy people. It can be psychologically disastrous.

Past medical history

The ankle swelling may not have justified diuretic treatment.

Drug and allergy history

The diuretic is likely to be contributory but not the full reason for incontinence.

Family history

It is unlikely that this is relevant in this case.

Social history

Incontinence can be the cause of huge embarrassment and social isolation.

Discussion

What are the neurological inputs to bladder control?

Bladder control has three main inputs:

- Parasympathetic, via S2–4 and the pelvic nerves, prompting detrusor contraction and sphincter relaxation hence promoting micturition
- Sympathetic, via T10–L2 and the hypogastric nerves, which does the opposite
- Voluntary or somatic, via the pudendal nerves, allowing contraction of a striated muscle sphincter.

SUMMARY BOX – ASSESSMENT AND PLAN

- ◆ Assessment should include a full examination, e.g. bladder volume, atrophic vaginitis.
- ◆ Investigations should include urinalysis and culture, ultrasound and urodynamics.
- ◆ Furosemide should be stopped.
- ◆ This is likely to be an overactive bladder and treatment could be with an anticholinergic, e.g. oxybutynin, imipramine, propiverine, tolterodine, trospium. Some anticholinergics are more likely to provoke confusion (trospium and solifenacin may be less likely as they do not cross the blood–brain barrier), and all can make outflow obstruction worse; they take weeks to months to work.

What are the principles of urodynamic studies?

Urodynamics involves catheterising the bladder (to obtain vesical pressure) and the rectum or vaginal fornix (to obtain abdominal pressure). Vesical pressure minus abdominal pressure gives a value for detrusor pressure. The bladder is filled at a non-physiological rate with a large volume of warm saline, which creates high pressures and flow rates can be recorded as a patient micturates. Pre- and post-micturition volumes, determined by ultrasound, aid urodynamics in determining a cause. For example in obstruction, there may be a very large residual of 800 ml on ultrasound with a low flow rate of 10 ml/s on urodynamics. Some normal values are:

- Normal bladder capacity 400–450 ml. Tolerance of this capacity decreases with age, so that an older person may have a tolerance capacity of only 100 ml, for example. Older people tend to get to know the locations of toilets because the time from urge to getting to a toilet without incontinence decreases.
- Normal residual volume < 50 ml (up to 100 ml in elderly).
- Physiologically the bladder fills at around 2 ml/min.
- Normal flow rates ≥ 14 ml/min (usually significantly higher). Urodynamic studies employ a fast flow rate such as 50 ml/min (100 ml/min would provoke instability in a healthy bladder).

What do you know about prostate-specific antigen (PSA) testing?

PSA levels vary with prostate size, and normal prostate cells contain PSA. Indeed, prostate cancer cells do not produce much PSA. It is possible to have advanced prostate cancer with metastases and a normal PSA, but usually the PSA that prostate cells contain leaks out easily and the PSA rises. Finasteride can reduce PSA levels with a danger

Table 2.111 Types of urinary incontinence

Type	Causes	Frequency	Symptoms	Management
Unstable, 'irritable' or overactive bladder – 'detrusor instability'	Abnormal bladder contractions (can occur in anyone at any time, not always provoking incontinence) Some patients have non-sustained contractions because of a 'myopathic' ageing bladder with big residual volumes	Most common cause	Urgency and frequency May be triggered by coughing or sudden movements Large volumes of urine (a flood)	Bladder retraining Anticholinergics Botulinum toxin A Surgery, e.g. clam ileocystoplasty, ileal conduit
Bladder neck (sphincter) / pelvic floor weakness ('stress incontinence')		Common	Small volumes of urine (a leak) Triggered by coughing or sudden movements / activity *A rule of thumb is that stress incontinence occurs when getting out of a chair, whereas detrusor instability causes the urge to get out of the chair!* + / – vaginal dryness / soreness or prolapse	Pelvic floor muscle exercises Oestrogen, topically or systemically (transdermal), in lower doses than used for hormone replacement therapy, suitable in post-menopausal patients with vaginal atrophy Surgery for prolapse
Outflow obstruction	Benign prostatic hypertrophy Urethral structure Constipation	Common	Urinary retention + / – overflow incontinence Small volumes of urine	Examination (constipation, large prostate, palpable bladder) 5α-reductase inhibition (finasteride) reduces prostatic bulk but takes months to work Alpha blockers improve flow but not urgency Surgery
Neuropathic bladder	**Frontal bladder** Dementia Normal pressure hydrocephalus Stroke	Less common	Voiding of large volumes with residual urine	
	Spinal bladder Multiple sclerosis Trauma	Less common	Urinary retention + / – overflow incontinence Later bladder automatically contracts and voids small volumes but with incomplete emptying Associated constipation + / – reflex priapism	Long-term 12–14 G indwelling catheter changed every 3–6 months Leakage or bypassing does not necessarily mean a blocked catheter but may indicate bladder contractions forcing more urine out than can enter the catheter; anticholinergics may help. Infections treated only when symptomatic, and little place for antibiotic prophylaxis because of resistance
	Peripheral neurogenic (non-contracting 'atonic') bladder Cauda equina lesions, e.g. central lumbar disc protrusion Peripheral nerve lesions e.g. diabetes	Least common	Painless distension of flaccid bladder with overflow incontinence and large residual volumes (i.e. continuous dribbling form large bladder whose fullness is not appreciated) Associated faecal incontinence, reduced anal tone and saddle anaesthesia	Intermittent self-catheterisation Long-term 12–14 G indwelling catheter changed every 3–6 months

Management is usually a case of doing a lot of simple things well. The goal is patient-determined. Management may include:

- Avoiding bladder irritants
- Rationalising drugs
- Bladder retraining (holding on successfully for 2minutes more each time) for urge or stress incontinence
- Antimuscarinic drugs for urge incontinence and overactive bladder (solifenacin or trospium in preference to oxybutynin in older people since oxybutynin may induce cognitive impairment)
- Botox or sacral nerve stimulation
- Pelvic floor muscle training

of unwarranted reassurance. PSA is usually very high in prostate cancer with soft-tissue metastases.

What treatment options are there for prostate cancer?

These include:

- Watchful waiting
- Radical prostatectomy with radical radiotherapy (can cure, or 'buy' 10 years of life if not curative); contemplated in fit patients with a normal rectal examination and a near normal PSA and diagnosis confirmed by transurethral ultrasound and biopsy
- Hormonal treatment if PSA high or metastases, e.g. bicalutamide (Casodex), goserelin (Zoladex)
- Intermittent androgen blockade, combined androgen blockage or stilboestrol.

CASE 2.46 RAISED INFLAMMATORY MARKERS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Ms Clarissa Dillon, aged 43 years
>
> Thank you for seeing this lady who has a raised plasma viscosity of uncertain cause. She has felt tired and unwell for around 4 months, and routine blood tests showed the following: haemoglobin 11.0 g/dl, white cell count and platelet count normal, plasma viscosity 2.3 (normal < 1.65), erythrocyte sedimentation rate 40 mm/h, C-reactive protein 28 mg/l, liver and renal function normal.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Ms Clarissa Dillon is a 43-year-old woman who for the last few months has felt lethargic and unwell to the extent that she has been unable to pursue a full day's work as a primary school teacher. She is a sensible woman who insists she is not 'making her symptoms up'. She has also had slightly more loose stools over this time period, on one or two occasions mixed with blood. She is usually well although she does have a heart murmur (mitral valve prolapse with mild regurgitation) for which she attends the cardiac clinic every 2 years. She does not smoke or drink alcohol. Six months ago she was in a road traffic accident in which she lacerated her wrist but she made a full recovery. She lives alone, and reports no stress at work. She is understandably concerned that her blood tests have been abnormal.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

The differential diagnosis of raised inflammatory markers is wide and essentially similar to those of pyrexia (Case 2.48). A full systematic enquiry here is essential.

Patient perspective

She is sensible and her concerns are entirely reasonable. The raised inflammatory markers and slightly low haemoglobin would dissuade from considering this to be chronic fatigue syndrome.

Past medical history

The history of a heart valve lesion cannot be ignored.

Drug and allergy history

Not relevant here.

Family history

A family history of colorectal cancer should be explored.

Social history

Her occupational history is unlikely to be relevant aetiologically and while sources of stress should be explored these are not likely to explain her new symptoms.

Discussion

Does the immune system just respond to infection?

It evolved to combat traditional threats, notably infection and natural surveillance against tumours (especially of oncogenic virus origin). It may respond to self-antigens (tolerance versus autoimmunity).

What types of immunity do you know of?

The immune system can elicit *innate* responses involving neutrophils, natural killer cells and complement and

SUMMARY BOX – ASSESSMENT AND PLAN

Further investigation is warranted. The two possibilities that immediately need to be considered are inflammatory bowel disease and infective endocarditis, the latter perhaps less likely given that her open injury was 6 months ago. Investigations that might be considered for any patient with raised inflammatory markers are listed below:

- Full blood picture
- Urea, creatinine and electrolytes, glucose
- Liver function tests
- Bone chemistry
- Thyroid function tests
- Plasma viscosity, erythrocyte sedimentation rate, C-reactive protein
- Immunoglobulin profile
- Serum electrophoresis for monoclonal band / paraproteinaemia
- Urine for light chains
- Antinuclear antibodies / rheumatoid factor / extractable nuclear antigens / antineutrophil cytoplasmic antibodies
- Serum angiotensin-converting enzyme
- Chest X-ray
- Abdominal ultrasound
- Chest, abdominal and pelvic computed tomography scan (?intra-abdominal solid tumour, lymphoma)
- Skeletal survey and bone marrow aspiration (if monoclonal band)
- Isotope bone scan (if bone pain or abnormal bone chemistry)
- Oesophagogastroduodenoscopy (if dyspepsia, upper gastrointestinal alarm symptoms or iron deficiency anaemia)
- Colonoscopy (note that a significant proportion of patients with iron deficiency anaemia and an upper gastrointestinal cause will have a concomitant colorectal lesion).

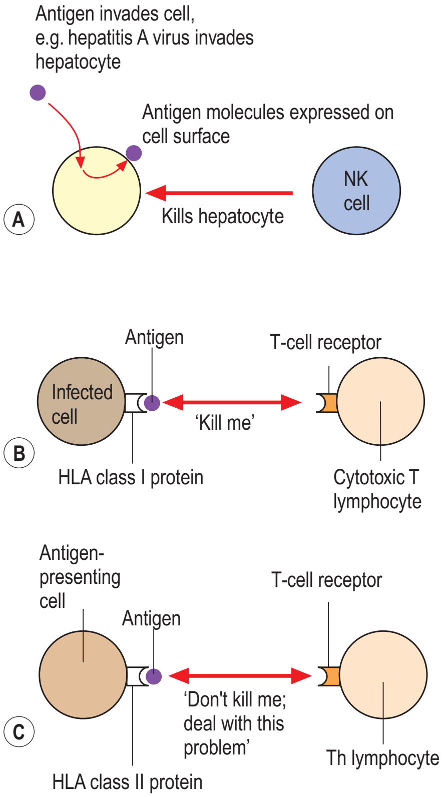


Figure 2.16 Responses to antigen: (A) natural killer (NK) cell killing, (B) cytotoxic T-lymphocyte response, (C) T-helper lymphocyte response. HLA, human leucocyte antigen.

acquired specific or adaptive responses involving T and B lymphocytes. The concepts of cell-mediated and humoral (antibody-mediated) immunity are now better replaced with appreciation of T-helper (Th) lymphocyte differentiation and T-cell and B-cell collaboration. Primary lymphoid organs are the thymus and bone marrow. Stem cells destined to become T and B lymphocytes arise in bone marrow. T lymphocytes migrate to the thymus and B lymphocytes remain in the bone marrow and both undergo maturation at these primary lymphoid sites. Secondary lymphoid organs are the lymph nodes and spleen and mucosa-associated lymphoid tissue (MALT). Lymphocytes in the lymph nodes respond to tissue antigens, the spleen to blood antigens and MALT to mucosal antigens.

How does the immune system first respond to antigens?

Antigens may be exogenous (micro-organisms) or endogenous (tumour proteins, transplant grafts, autoantigens). When an antigen invades a host cell it is processed such that some antigenic peptide is expressed on the host cell surface. Natural killer cells, which are large granular lymphocytes, may kill such a cell, but tend to leave damage in their wake (Fig. 2.16A). They will not seek out and destroy every last antigen and have no memory. For reliable elimination of infection a more eloquent and specific response is required.

Why is the major histocompatibility complex (MHC) important?

Also termed the human leucocyte antigen (HLA) complex, this is a segment of genes on chromosome 6 that encode MHC (HLA) molecules that are expressed on the surface of cells. Their four-subunit structure forms a cradle or peptide-binding groove in which antigenic peptide derived from infection may be presented to a cytotoxic T lymphocyte or a Th lymphocyte. Each MHC molecule presents a specific antigenic peptide and an immune response is only triggered in the presence of the MHC molecule – such immune responses are said to be antigen-specific and MHC-restricted. Some diseases are associated with certain HLA variants such as B27 with seronegative arthropathies, DR2 with narcolepsy, DR4 with rheumatoid and B8, DR3 with many organ-specific autoimmune diseases. The HLA complex is highly polymorphic between individuals, resulting in a unique HLA or tissue type.

How does the MHC–peptide complex initiate a specific (adaptive) immune response by cytotoxic and Th lymphocytes?

The MHC–peptide complex acts as a distress signal to either cytotoxic or Th lymphocytes.

MHC class I–peptide complex distress signal

MHC A, B and C genes encode MHC class I molecules (containing β_2-microglobulin) that are present on virtually all cells in the body. The *MHC class I–peptide complex on an infected cell is engaged by the T-cell receptor of a cytotoxic T lymphocyte* (also known as a CD8 cell), an interaction that *leads to killing of the infected cell by the cytotoxic T lymphocyte*. The MHC class I distress signal, capable of being elicited by most cells in the body, essentially says *'kill me'* (Fig. 2.16B).

MHC class II–peptide complex distress signal

MHC DP, DR and DQ genes encode MHC class II molecules that are present only on antigen-presenting cells (APCs), which are mostly macrophages. MHC class II molecules are inducible, their genes upregulated in response to antigen. The *MHC class II–peptide complex on the APC is engaged by the T-cell receptor of a Th lymphocyte* (also known as a CD4 cell), an interaction that *leads to Th-lymphocyte activation and differentiation*. The MHC class II distress signal essentially says *'don't kill me, but deal with this problem'* (Fig. 2.16C).

MHC class I cytotoxic responses are very good at dealing with intracellular antigens. But MHC-class-II-driven Th responses are better for eliminating extracellular organisms. Helminths, for example, are too big to be phagocytosed and so APCs take a snippet of worm and present it as antigen to Th cells, which then decide what to do with it. This said, many bacteria, fungi and intracellular organisms also require a Th response.

How are Th cells activated?

Two signals are needed for activation (Fig. 2.17): the first between the MHC class II–peptide complex and the T-cell receptor (TCR; CD3) of the Th cell (the almost infinite permutations of TCR gene rearrangement allowing the TCR to respond to an almost infinite variety of antigens) and a second *co-stimulatory signal*. Without the latter, the Th lymphocyte remains inactive or naive, a state known as anergy. There are many co-stimulatory signals, but that between APCs and TCRs is the B7–CD28 interaction.

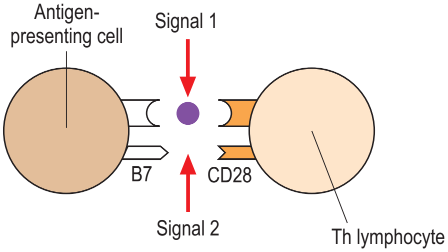


Figure 2.17 T-helper (Th) lymphocyte activation.

There must also be immunological 'brakes' to Th activation otherwise lymphoproliferation would continue unchecked. One brake is cytotoxic T-lymphocyte antigen-4 (CTLA4), induced simultaneously with CD28 but with inhibitory rather than stimulatory activity. It may be aberrant in some lymphoproliferative disorders.

What do we mean by Th1 and Th2 pathways? (Fig. 2.18)

Cytokines produced by APCs during the activation process of Th lymphocytes direct whether naive (Th0) lymphocytes differentiate into Th1 or Th2 lymphocytes and thus down a Th1 or Th2 pathway. The cytokine interleukin-12 (IL-12) stimulates a Th1 response and IL-4 stimulates a Th2 response. The elected pathway depends upon numerous factors, including the nature of the antigen. Th1 and Th2 lymphocytes in turn secrete characteristic groups of cytokines that induce proliferation of Th lymphocytes along the designated Th1 or Th2 pathway. Th1 lymphocytes secrete IL-2 and interferon-γ (IFN-γ) and Th2 lymphocytes secrete IL-3, -4, -5, -10 and -13. An effective immune system that does not result in 'friendly fire' relies on a well-balanced Th1–Th2 environment. Homeostasis is achieved by switch-off mechanisms and self-perpetuation mechanisms by cross-inhibition – IFN-γ inhibits the Th2 pathway and IL-10 inhibits the Th1 pathway.

What are cytokines?

Cytokines are molecules secreted by cells telling other cells what to do. There is a huge array of cytokines, and groups include ILs (secreted by leucocytes and acting on leucocytes), IFNs, tumour necrosis factors (TNFs), chemokines (chemotactic) and colony-stimulating factors, promoting haematopoiesis. Most cytokines have multiple roles or effects. If one cytokine is absent, another may take its place. Cytokines are only produced by activated cells and are secreted locally. They bind with cytokine receptors on cells nearby. Cytokine receptors comprise polypeptide subunits with intra- and extracellular domains. One subunit, the common γ-chain, is common to receptors for several ILs. While cytokines will stand in for absent colleagues, cytokine receptors have no back-up. Mutations of the γ-chain occur in X-linked severe combined immunodeficiency (SCID), with loss of function of several cytokine receptors; 'combined' implies that both T-cell and B-cell receptors are affected.

Just as there is a huge array of cytokines and cytokine receptors, there is a huge array of intracellular pathways. One such is the Jak (Janus kinase) and STAT (signal transducers and activators of transcription) pathway. Jaks are tyrosine kinases. After cytokine binding, a phosphorylation cascade of Jaks and STATs enables STATs to translocate to the nucleus, bind to DNA and act as transcription factors. Thus, mutations of Jak are another cause of SCID.

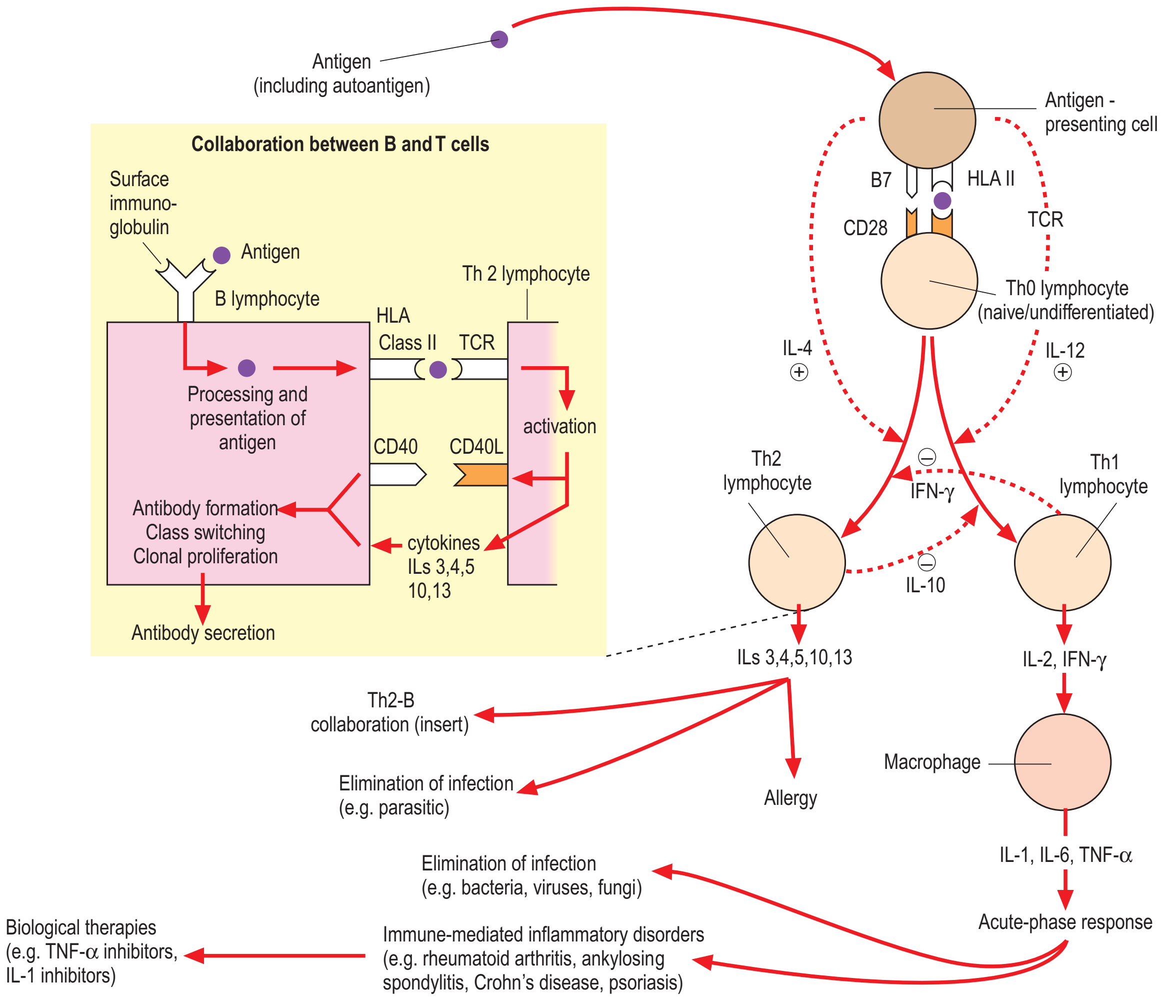

Antigen
(including autoantigen)
Antigen -
presenting cell
B7
HLA II
CD28
TCR
Th0 lymphocyte
(naive/undifferentiated)
IL-4
⊕
IL-12
⊕
⊖
IFN-γ
⊖
IL-10
Th2
lymphocyte
Th1
lymphocyte
ILs 3,4,5,10,13
IL-2, IFN-γ
Macrophage
IL-1, IL-6, TNF-α
Acute-phase response
Collaboration between B and T cells
Surface
immuno-
globulin
Antigen
B lymphocyte
Th 2 lymphocyte
HLA
Class II
TCR
Processing and
presentation of
antigen
activation
CD40
CD40L
Antibody formation
Class switching
Clonal proliferation
cytokines
ILs 3,4,5
10,13
Antibody secretion
Th2-B
collaboration (insert)
Elimination of infection
(e.g. parasitic)
Allergy
Elimination of infection
(e.g. bacteria, viruses, fungi)
Biological therapies
(e.g. TNF-α inhibitors,
IL-1 inhibitors)
Immune-mediated inflammatory disorders
(e.g. rheumatoid arthritis, ankylosing
spondylitis, Crohn's disease, psoriasis)

Figure 2.18 T-helper 1 lymphocyte and T-helper 2 lymphocyte pathways. HLA, human leucocyte antigen; IFN, interferon; IL, interleukin; TCR, T-cell receptor; Th, T-helper; TNF, tumour necrosis factor.

What is the role of the Th1 response?

This is pro-inflammatory. Th1 lymphocytes secrete cytokines, notably IL-2 and IFN-γ, that powerfully propagate the Th1 pathway (IL-2 induces Th1 cell proliferation and IFN-γ inhibits the rival Th2 pathway) and stimulate macrophages, which in turn synthesise and secrete the inflammatory cytokines IL-1, IL-6 and TNF-α (Fig. 2.18) that mediate the acute-phase response. B lymphocytes may also be stimulated, although the Th2 pathway is the major instigator of B-lymphocyte activity and antibody synthesis. If unchecked, chronic inflammation can ensue, and ultimately healing with fibrosis mediated by fibroblast-stimulating cytokines such as transforming growth factor-β. This immune response typifies many bacterial, viral and fungal infections, antitumour activity and many immune-mediated inflammatory disorders.

What is the acute-phase response?

Many systemic changes associated with pro-inflammatory cytokines are recognised. These changes, collectively termed the acute-phase response, include hepatic synthesis and release of acute-phase proteins – complement proteins, coagulation proteins (including activated protein C), transport proteins and C-reactive protein (CRP). Some acute-phase proteins such as albumin decrease in concentration. Other acute-phase phenomena include fever, tachycardia, anorexia, rising concentrations of 'stress' hormones such as cortisol and catecholamines, decreased insulin-like growth factor 1 levels, anaemia of

Box 2.107 **Raised inflammatory markers**

The role of inflammatory markers

Measurement of inflammatory markers has two main functions:

- To detect acute inflammation that might indicate specific disease
- To give a marker of treatment response.

Measurement of inflammatory markers can also be used as a general, but non-specific, test for serious underlying disease.

Inflammatory markers

Inflammatory markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma viscosity, fibrinogen, ferritin, and several other acute-phase proteins, though only the first three are commonly referred to as inflammatory markers:

- CRP is considered particularly useful in detecting bacterial infection.
- Plasma viscosity is now generally preferred to ESR, as it is unaffected by anaemia or polycythaemia, or by delays between sampling and measurement, with results independent of age or sex. All these factors potentially affect the ESR, a time-honoured test for red cell rouleaux formation, but now considered unreliable because of factors that increase it (e.g. anaemia, macrocytosis, older age, female sex, pregnancy) and factors that decrease it (e.g. polycythaemia, microcytosis, spherocytosis, hypoproteinaemia).

Diagnostic testing for specific diseases

Diseases with prominent activation of the inflammatory response fall into three main groups:

- Infections
- Autoimmune diseases
- Some (particularly haematological) malignancies.

Interpreting an abnormal result is relatively straightforward if there is a clear pre-test hypothesis against which the test result can be evaluated, e.g. if assessing the likelihood of serious infection in a patient with fever. The main difficulty is in the interpretation of an incidental abnormality, when no specific disease is suspected.

Ruling out disease

Normal levels of inflammatory markers are valuable in ruling out a few specific conditions, notably polymyalgia rheumatica, giant cell arteritis, myeloma, and infection of hip revisions.

Other diseases causing raised inflammatory markers

Raised inflammatory markers may be found in many other conditions, particularly infections, autoimmune conditions and certain cancers. In such cases, they increase the probability of the condition being present, but additional information is needed to be confident disease is present or absent. Inflammatory markers are too non-specific to be useful for diagnosing serious disease and should rarely be used in this situation. Inflammatory markers may have value as part of a clinical prediction rule for a particular condition incorporating other features.

Incidental finding of raised inflammatory markers

Inflammatory markers are sometimes used as a general marker to differentiate between the presence and absence of disease but generally, when inflammatory markers are tested for non-specific purposes, the results are of little or no value. 'Incidental' raised inflammatory markers are difficult to interpret and can lead to expensive and potentially harmful investigations. In an incidental finding, if history and examination yield no clues as to cause, it is usually reasonable to wait and see if symptoms develop.

If levels are markedly raised (such as ESR > 100 mm / h), the likelihood of disease is much higher, but history, examination and focused investigations are usually sufficient to establish a diagnosis.

chronic disease, leucocytosis, thrombocytosis, catabolism and cachexia.

What is the value of testing inflammatory markers – CRP, erythrocyte sedimentation rate (ESR) or plasma viscosity?

The role of inflammatory markers is discussed in Box 2.107.

What are immune-mediated inflammatory disorders?

These are diseases driven by a Th1 response, e.g. rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriasis.

What is the role of the Th2 response?

The Th2 response regulates the intensity of Th1 responses, dampening down the tendency to inflammation through the negative stimulus of IL-10. In this non-inflammatory respect, the Th2 pathway is 'anergic', although it is not anergic in the true sense of the word in that considerable activity is afoot!

Another major role of Th2 lymphocytes is collaborating with B cells in the production of specific antibodies (which are good at eliminating extracellular antigens such as encapsulated bacteria). While B lymphocytes can produce antibodies by direct stimulation from an antigen, Th2–B lymphocytes collaboration is the more usual, optimal and efficient means of antibody production.

When an antigen stimulates a B lymphocyte, that B lymphocyte has the capacity to act as an APC to Th2 lymphocytes via an MHC class II–peptide complex expressed on its surface (exactly analogous to a macrophage APC presenting an MHC class II peptide to a Th lymphocyte). Again, a co-stimulatory signal is required, in this case CD40–CD40 ligand. The interaction leads to release of Th2 effector cytokines (IL-3, -4, -5, -10 and -13) that feed back to the B lymphocyte (Fig. 2.18) and promote class switching, clonal proliferation, differentiation to plasma cells and antibody production.

Only some B cells become antibody-secreting plasma cells dedicated to the current threat. Others undergo identical specific somatic rearrangement of their immunoglobulin genes and then sit back as memory cells, armed and ready for any future secondary attack. T cells can similarly survive as memory cells.

IL-3 is also notorious for causing release of histamine from mast cells, IL-4 for stimulating immunoglobulin E production and IL-5 for stimulating eosinophils. These are of course central to parasite elimination, and the Th2 pathway is active in parasite infection. These are also central to atopy and allergy, which are characterised by an excessive Th2 response.

Do you know of any diseases that may have two presentations, depending upon which of the Th1 or Th2 pathways predominates?

There are many. Examples are leprosy (tuberculoid – Th1 response causes intense granulomatous inflammation, overt symptoms and effective organism elimination; lepromatous – Th2 response leads to persistence of organism), neurocysticercosis and sarcoidosis (erythema nodosum highly inflammatory and lupus pernio more anergic).

What are chemokines?

Chemokines (chemotactic cytokines) are cytokines that direct or attract leucocytes to sites of inflammation or injury. They are essential in evoking an adequate immune inflammatory response, but may also contribute to disease pathogenesis and are now potential targets for disease modification, such as chemokine receptor antagonists (Table 2.112 – for reference only!). Chemokines work with adhesion molecules called selectins and integrins in seducing leucocytes down extravasation pathways from blood to tissues.

What do understand by the term immune-modulatory therapies?

Immune-modulatory therapies may boost, suppress or deviate the immune response. Other than vaccination, most agents are used to suppress immune responses.

More traditional therapies

These include corticosteroids, cytotoxic agents that inhibit DNA synthesis (cyclophosphamide, mycophenolate, azathioprine, methotrexate) and inhibitors of intracellular signalling pathways such as ciclosporin and tacrolimus.

Molecular therapies

There is now a wide range of molecular therapies or 'biologics'. There is a general system of nomenclature (e.g. 'mab' = monoclonal antibody; 'xi' = mouse derived; 'hu' = human derived; 'tu' = antitumour), and so we have agents such as rituximab, where only the first few letters are unique. Examples of therapies are given in Table 2.113.

What is haemophagocytic syndrome?

The term haemophagocytosis refers to the unusual problem in which activated macrophages engulf red cells, white cells, and platelets and their precursors. Haemophagocytic lymphohistiocytosis, the prototype haemophagocytic syndrome, is a condition of uncontrolled activation of the cellular immune system, mediated by numerous cytokines including IL-1, IL-2, soluble IL-2 receptor, plasminogen activator and prostaglandins. The cause is usually infection (viral, bacterial, fungal or protozoal) or autoimmunity including the connective tissue disorders, but may be malignancy or familial. Still's disease may provoke macrophage activation syndrome, associated with very high inflammatory markers including ferritin. Clinical features include fever, splenomegaly, cytopenias, hypofibrinogenaemia and rash, in the presence of haemophagocytosis.

What do immunoglobulins do?

During development in the bone marrow, virginal B cells contain 'unmutated' immunoglobulin V region genes. These genes undergo appropriate somatic mutation in response to antigen encounters in peripheral lymphoid sites, and B cells subsequently survive as memory cells in the lymph nodes or circulation, or undergo isotype class switching to become antibody-producing plasma cells. Immunoglobulins (or antibodies) precipitate antigens and activate complement proteins, the role of complement being to eliminate precipitated antigens and immune complexes.

What are cryoglobulins?

A cryoglobulin is simply any antibody that precipitates in the cold (at < 4 °C). It dissolves when warmed to 37 °C. Cryoglobulins may be immunoglobulin G (IgG), IgM or IgA, and may be *monoclonal* IgM or IgG, tending to form precipitates (cryoprecipitation), *mixed* (usually monoclonal IgM directed against polyclonal IgG) or *polyclonal* (mixtures of polyclonal IgM and IgG). Mixed and polyclonal cryoglobulins tend to form immune complexes with antigens. Cryoglobulins, especially monoclonal, are often associated with lymphoproliferative disease and polyclonal with autoimmune disease such as systemic lupus erythematosus and infections such as hepatitis C. Cryoglobulinaemia may result in vasculitis, occlusive vascular disease and Raynaud's phenomenon.

What are cold agglutinins?

These are IgM antibodies that cause red blood cells to aggregate at < 37 °C. They may be found in *Mycoplasma*, coxsackievirus and malarial infections and in lymphoproliferative disease. It is not surprising (given that both cryoglobulins and cold agglutinins are merely immunoglobulins secreted from plasma cells) that cryoglobulinaemia and cold agglutination are much more common in diseases of plasma cell proliferation. They merely represent a proportion of the immunoglobulin production in

Table 2.112 Chemokines, their roles, and disease examples

Chemokine family	Broad role of that family of chemokines	Chemokine receptors	Examples of chemokines attracting cells bearing those chemokoine receptors	Examples of cells bearing chemokine receptors	Disease associations
CC First two of four cysteine residues adjacent	Attract mononuclear cells to sites of chronic inflammation, e.g. trauma, bacterial infection, ischaemia, chronic inflammatory disease	CCR1	Macrophage inhibitory protein MIP-1α (CCL3) RANTES (CCL5)	T cells Monocytes	Rheumatoid arthritis Multiple sclerosis
		CCR2	Monocyte chemoattractant proteins or MCP 1–4 (CCL2, 8, 7, 13)	Monocytes Macrophage antigen-presenting cells Memory T cells	Atherosclerosis Rheumatoid arthritis Multiple sclerosis Type 2 diabetes
		CCR3	Eotaxins (CCL11, 13) MCP2–4 RANTES	Eosinophils Mast cells Th2 cells	Asthma and allergy
		CCR4	Thymus and activation regulated chemokine or TARC (CCL17) Macrophage-derived chemokine or MDC (CCL22)	Th2 cells	Parasite infection Graft rejection T-lymphocyte attraction to skin
		CCR5	MIP-1α MIP-1β (CCL4) RANTES	T cells Monocytes	HIV requires CD4 and co-receptor CCR5 recognition to enter macrophages
		CCR6	CCL20	T cells B cells Antigen-presenting cells	Mucosal humoral immunity T-lymphocyte attraction to intestine
		CCR7	CCL19 CCL21	CCR7 on antigen-presenting cells and T cells CCL19 and CCL21 on endothelium and inside lymph nodes attract peptide-bound antigen-presenting cells and T cells for subsequent antigen-presenting cell–T-cell engagement B cells also upregulate CCR7 expression to interact with Th cells After immune response subsides, CCR7 memory T cells continuously patrol tissues and lymph nodes via the bloodstream, some specialised for defending the skin or gastrointestinal tract	Exuberant chronic inflammation

Table 2.112 Chemokines, their roles, and disease examples—cont'd

Chemokine family	Broad role of that family of chemokines	Chemokine receptors	Examples of chemokines attracting cells bearing those chemokoine receptors	Examples of cells bearing chemokine receptors	Disease associations
		CCR8	CCL1	Th2 cells Monocytes Macrophage antigen-presenting cells	Granuloma formation
		CCR9	CCL25	T cells	Inflammatory bowel disease
		CCR10	CCL27	T cells	
CXC Single amino acid residue between first two cysteines	A subgroup of CXC chemokines with a glutamate–leucine–arginine motif (designated ELR+ chemokines)	CXCR1	Interleukin-8 (CXCL8)	Neutrophils Monocytes	Inflammatory lung disease COPD
	Notably attract neutrophils to sites of acute inflammation, induce granulocyte exocytosis and contribute to wound repair, e.g. interleukin-8 (CXCL8) attracts neutrophils to areas of acute inflammation and binds neutrophil receptors CXCR1 and CXCR2 to each other Inflammatory mediators such as IL-1, TNF-α and bacterial lipopolysaccharides elicit production of CXC chemokines	CXCR2	Interleukin-8 CXCL1–3,5,6	Neutrophils Monocytes Endothelial cells	Inflammatory lung disease COPD Angiogenic factor for tumour growth
		CXCR3-A	CXCL4, 9, 10, 11	Th1 cells Mast cells Mesangial cells	Inflammatory skin disease Multiple sclerosis Transplant rejection
		CXCR3-B	CXCL4, 9–11	Endothelial cells Neoplastic cells	Angiostatic for tumour growth
		CXCR4	CXCL12	Wide expression	HIV requires CD4 and co-receptor CXCR4 recognition to enter T lymphocytes
		CXCR5	CXCL13	B cells	
		CXCR6	CXCR16	Mediates interaction between antigen-presenting cells and T cells Scavenger-receptor activity for oxidised lipids	Inflammatory liver disease May participate in atherosclerosis
CX_3C	CX_3CL1 arrests cells under normal physiological flow and may be cleaved from endothelium to act as soluble chemokine		CX_3CL1 (fractalcine)	Macrophages Endothelial cells Smooth muscle cells	Atherosclerosis
XC Single cysteine residue			XCL1 (lymphotaxin)	T cells Natural killer cells	Rheumatoid arthritis IgA nephropathy

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; Ig, immunoglobulin; RANTES, regulated on activation normal T-cell expressed and secreted; Th, T helper; TNF, tumour necrosis factor.

Table 2.113 Molecular therapies

	Action	Examples of indications	Toxicity
Agents directed at cytokines			
Infliximab Adalimumab Certolizumab Golimumab	Inhibit TNF-α: anti-TNF-α antibodies	Rheumatoid arthritis Ankylosing spondylitis Psoriasis / psoriatic arthropathy Inflammatory bowel disease	Injection / infusion reactions Infection Malignancy Lupus-like conditions (relative or absolute contraindications to anti-TNF therapy may be memorised by the mnemonic STOIC–sepsis, tuberculosis, optic neuritis, infusion reaction, cancer)
Etanercept	Inhibits TNF-α: TNF receptor p75–IgG Fc fusion protein		
Ustekinumab	Anti-IL-12 and IL-23	Psoriasis	
Denosumab	Anti-RANK ligand: inhibits RANK-mediated osteoclast differentiation and function	Osteoporosis	
Agents directed at cell surface antigens			
Rabbit antithymocyte globulin	Depletes lymphocytes and modulates T-cell activation and migration	Allograft rejection	
Basiliximab: anti-CD25	Inhibits T-cell proliferation by blocking IL-2R chain molecules	Allograft rejection prophylaxis	
Abatacept: CTLA4-Ig	Reduces T-cell activation by blocking T-cell co-stimulation	Rheumatoid arthritis	
Rituximab: anti-CD20	Depletes mature B cells (plasma cells preserved so can still produce antibodies to previously encountered infections)	Lymphoma Rheumatoid arthritis	
Natalizumab: anti-α4 integrin	Inhibits T-cell migration by inhibiting an integrin adhesion molecule	Highly active relapsing–remitting multiple sclerosis Rheumatoid arthritis	
Tocilizumab: anti-IL-6 receptor	Reduces macrophages, T cells and B cells and neutrophil activation	Rheumatoid arthritis	
Alemtuzumab: anti-CD52, Campath	Selectively depletes mature B and T cells	Chronic lymphocytic leukaemia Multiple sclerosis	
Other	Molecular therapies against a widening range of small molecules such as JAKs	A widening range of conditions	

Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; RANK, receptor activator of nuclear factor-κB; TNF, tumour necrosis factor.

these diseases. They may also be found in otherwise healthy people, especially older people.

What are complement proteins?

The complement system is a cascade of plasma proteins, synthesised in the liver, whose role is to remove antigen precipitates and immune complexes (antigen–immunoglobulin complexes). The complement system may be activated by one of two routes: the classical pathway or the alternative pathway. The common result of both pathways is cleavage of the complement protein C3.

What do you understand by the term hypersensitivity?

This refers to excessive immune responses (Table 2.114).

What are urticara, angioedema and anaphylaxis?

Early experiments using sea anemone stings to dogs (poor lovely dogs!) revealed that subsequent exposure could produce rapid death. Hypersensitivity or hypersusceptibility refers to reproducible symptoms to a defined stimulus. Mechanisms may be non-allergenic or allergenic, and in the latter immune responses are key and may be IgE mediated (atopic or non-atopic such as food or venom induced) or non-IgE mediated such as eosinophil or T-cell related.

Urticaria and angioedema

This is a ruby red, raised itchy rash from vasodilation and increased blood flow and vascular permeability caused by mediator release from mast cells. Urticaria occurs in the superficial dermis while angioedema is localised deep tissue swelling. Urticaria and angioedema may occur together and as part of an anaphylactic reaction, but either may occur alone. They may be due to IgE mechanisms, but most is non-IgE mediated.

Anaphylaxis

Anaphylaxis is a systemic reaction, severe and life threatening, with smooth muscle contraction and blood vessel changes. Symptoms include any of rhinitis, conjunctivitis,

Table 2.114 Hypersensitivity reactions

Type	Problem	What happens	Examples
I	Anaphylaxis	Antigens react with IgE on mast cells leading to release of vasoactive substances including histamine and leukotrienes Reaction within minutes of exposure in previously sensitised individuals	Anaphylaxis
II	Antibody-dependent cytotoxicity	Cell surface antigens react with circulating antibody triggering complement activation	Transfusion reactions Hyperacute transplant rejection
III	Immune complex mediated	Circulating antigens react with circulating antibodies	Extrinsic allergic alveolitis Serum sickness Post-infectious glomerulonephritis
IV	Cell-mediated immunity: delayed hypersensitivity	Antigens, in association with HLA class II molecules on APCs, are presented to already sensitised (memory) Th lymphocytes	Tuberculin reaction Contact dermatitis Graft versus host disease Graft rejection

APC, antigen-presenting cell; HLA, human leucocyte antigen; IgE, immunoglobulin E; Th, T helper.

laryngeal oedema, angioedema, reactive pulmonary oedema, gastrointestinal disturbance, flushing and urticaria. It may produce hypotension and bronchospasm, where it is referred to as anaphylactic shock. It may be allergenic or non-allergenic, IgE or non-IgE mediated, but anaphylaxis due to IgE antibodies (type 1 hypersensitivity) is the most severe form of immediate allergic reaction. The immune system must have been previously exposed to the allergen for IgE antibodies to form and anaphylaxis to occur. Similar reactions can be caused by substances that directly activate mast cells without the presence of specific IgE antibodies (previously termed anaphylactoid reactions) such as strawberries, radiographic contrast and opiates, or by direct ingestion of histamine from substances such as tomatoes and shrimps or foodstuffs bacterially contaminated (scromboid reactions). Causes of anaphylaxis include:

- Drugs (commonly anaesthetics, β-lactams, contrast agents, gelatine infusions, angiotensin-converting enzyme inhibitors, aspirin and non-steroidal anti-inflammatory drugs)
- Foods (commonly nuts, eggs, seafood and milk)
- Venoms (bees, wasps, scorpions); anaphylaxis is worse in people taking drugs such as non-steroidal anti-inflammatory drugs, but unlike drug and food anaphylaxis the repeated response to venoms may not be escalatory
- Pollens
- Animal dander.

Treatment of anaphylaxis includes epinephrine (adrenaline) (500 μg intramuscularly, repeated if necessary, with intensive therapy unit expertise if using intravenous epinephrine, often as 50 μg using the 1 : 10 000 preparation), hydrocortisone, crystalloid (not potentially anaphylaxis-inducing colloid), oxygen and β_2 nebulised bronchodilators. A serum tryptase activity blood sample at around an hour (peaks at 1 hour) and a subsequent sample to confirm it was raised may be useful. Observation in hospital for 24–48 hours is important, and before discharge issuing and training of an *Epipen* or *Anapen*, which contains 300 μg of epinephrine for intramuscular injection into the thigh.

C1 esterase inhibitor, hereditary angioedema and angiotensin-converting enzyme (ACE) inhibitors

Angioedema involves uncontrolled activity of bradykinin, and to an extent complement breakdown products such as C2 kinin and alterations in the coagulation cascade. Rarely, angioedema may be caused by defects in C1 esterase inhibitor. Hereditary angioedema is a very rare condition that can trigger bowel oedema. ACE inhibitors can provoke angioedema since ACE is important to bradykinin breakdown.

What is meant by atopy and allergy?

Atopy refers to a hereditary predisposition to high levels of IgE against common environmental proteins. Only a subset of these individuals will develop symptoms, or allergy. The distinction is important because skin prick tests and specific IgE blood tests will not diagnose allergy, only atopy.

How does allergy arise?

It is suggested that we are born with a Th2-weighted imbalance (to fight worms!) with IL-4 in natural domination, but that in the first few months of life exposure to diseases such as tuberculosis allows the emergence of Th1 to level the see-saw. Atopic predisposition seems to start in early life, with impaired IFN-γ production. Exposure to bacteria in early life may increase IFN-γ levels and lends weight to the 'hygiene' hypothesis, in which reduced exposure to bacteria, antibiotics and certain infant diets results in the persistence of a dominant Th2 pathway. Mycobacterial species are known to stimulate powerful IFN-γ production and research has examined vaccines to promote switching from Th2 to Th1 pathways.

How does tolerance give way to autoimmunity?

Immune responses to antigens and autoimmune responses to auto (self) antigens involve the same mechanisms. What is remarkable is how the immune system determines what is foreign and what is self. It does not normally respond to self-antigens, and this state of affairs is called tolerance. Tolerance is not fully understood. It begins in embryonic life, when lymphocytes 'learn' to react to antigens during their production in the thymus, bone marrow and lymphoid organs. Their developing cell receptors undergo random gene rearrangement in preparation for the diverse array of exogenous antigens in postembryonic life, and every T cell has a specific TCR encoded by a specific T-cell gene rearrangement. Understandably, during development, TCRs will encounter self-antigens. At this stage, any strong interactions between TCR and self-antigen will lead to de-selection – lymphocytes with a tendency to 'friendly fire' are destroyed by apoptosis, or programmed cell death. However efficient this process, it is never enough to prevent some self-reacting lymphocytes from 'qualifying'. These dangerous cells, and their clonal offspring, must be kept in check by the immune system for the rest of an individual's life. One safeguard is called anergy. Anergy ensures the lack of response to a self-antigen by an autoimmune T lymphocyte unless a co-stimulatory signal is present. Most cells in the body are not competent to deliver such a signal. Another protective mechanism is ignorance. Frequently, autoimmune lymphocytes never encounter their respective self-antigens because the latter are 'hidden' behind cellular or vascular barriers. Equally, apoptosis ensures that, unlike necrotic cell death, antigenic intracellular contents do not spill out into the face of danger. Even these stealthy safeguards may fail, and the result is autoimmune disease.

CASE 2.47 POLYMYALGIA AND GIANT CELL ARTERITIS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mrs Muriel Gray, aged 82 years
>
> Thank you for slotting this lady in urgently. She has had a right temporal and occipital headache for the past 2 weeks and this is out of character for her. She is a usually fit and active lady whom I seldom see at the surgery. I am concerned about the possibility of temporal arteritis. Her erythrocyte sedimentation rate was 45. I have started 60 mg of prednisolone.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mrs Muriel Gray is an 82-year-old woman who for the past 2 weeks has had intermittent severe headaches over the right temporal area extending to the back of the neck. These have no diurnal pattern, are not related to posture or activity, and can be present at any time of the day or night. Her scalp is a little tender but not enough to stop her from washing or brushing her hair. She has not noticed any pain with chewing. She has no other symptoms. She has a past medical history of breast cancer with a mastectomy 4 years ago and remains on tamoxifen. She does not take any other medications. She feels a little better on prednisolone, which she has been taking for 3 days, but is very concerned about being on corticosteroids because her brother was on these for Crohn's disease and developed terrible osteoporosis. She is also concerned because her mother started to develop headaches at a similar age and turned out to have brain metastases from breast cancer. She lives with her husband and their dogs.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

The headache in giant cell arteritis (GCA) is classically temporal but potentially anywhere, relating to the diverse facial artery distributions. Up to 15% of GCA presents occipitally. Symptoms of GCA are outlined in Table 2.115 and you should explore these.

GCA can be easily missed when systemic symptoms (e.g. low-grade fever or weight loss), ischaemic symptoms (jaw claudication or transient visual symptoms), or polymyalgic

Table 2.115 Symptoms of giant cell arteritis (GCA)

Common symptoms and signs	Diagnostic criteria (American College of Rheumatology)	
Symptoms Abrupt-onset headache: usually unilateral and temporal, occasionally diffuse or bilateral Scalp pain: diffuse or localised; may lead to difficulty in combing hair Jaw and tongue claudication Visual symptoms: amaurosis fugax, blurring and diplopia Constitutional symptoms: fever, weight loss and tiredness Polymyalgic symptoms Limb claudication **Signs** Abnormal superficial temporal artery: tender, thickened or beaded, with reduced or absent pulsation Scalp tenderness Transient or permanent visual loss Visual field defect Relative afferent papillary defect Anterior ischaemic optic neuritis: pale, swollen optic disc with haemorrhages on fundoscopy Central retinal artery occlusion: unilateral or bilateral Upper cranial nerve palsies Features of large-vessel GCA: asymmetry of pulses and blood pressure, bruits (usually of the upper limb) **Predictive clinical features** No features have a high negative likelihood ratio, because no feature (even headache) is reliably present in all cases. Several symptoms are moderately predictive of a positive biopsy result: Jaw claudication (34%); claudicant pain comes on gradually during chewing, whereas temporomandibular pain or dental pain is immediate Diplopia (8%) Any abnormality on palpation of the temporal artery – absent, beaded, tender or enlarged (65%) Other useful predictive features are: Temporal headache Scalp tenderness ESR > 100 mm / h Anaemia	Without visual symptoms	≥ 3 of: Age > 50 years New-onset headache Temporal artery tenderness / decreased pulsation ESR > 50 mm / h Positive temporal artery biopsy
	With visual symptoms	Urgent ophthalmology review

Differential diagnoses
Herpes zoster
Migraine or other causes of headaches
Serious intracranial pathology causing, for example, headache and raised inflammatory markers
Other causes of acute vision loss, e.g. transient ischaemic attack
Cervical spine disease
Ear, nose and throat pathology, e.g. sinus disease, temporomandibular joint disturbance

ESR, erythrocyte sedimentation rate.

symptoms (proximal myalgia or morning stiffness) predominate over the well-known hallmark of temporal headache. GCA occasionally presents with vascular occlusive disease elsewhere, e.g. chest pain, or as acute confusion with raised inflammatory markers in an elderly person.

Patient perspective

Her fears of steroids are not unfounded and should be respected by outlining that:

- You will seek to establish the diagnosis quickly and the need or otherwise for these to continue
- You would recommend that she remains on these until then because GCA responds very well to steroid treatment but is potentially sight-threatening and stroke-provoking without
- You would start medication to protect the bones if it becomes necessary to recommend continuing steroids after further tests
- Steroids are gradually weaned in GCA.

Past medical history

The history of breast cancer brings brain metastases into the differential diagnosis of her headaches.

Drug and allergy history

This is less relevant in this case.

Family history

There are no suggestions of a familial illness other than possible breast cancer, although this patient was only diagnosed with breast cancer in recent years.

Social history

Explore her active lifestyle, what her symptoms limit her from doing and whether the steroids have helped with some of these activities.

SUMMARY BOX – ASSESSMENT AND PLAN

- The two important differential diagnoses are giant cell arteritis and metastatic breast cancer.
- Urgent investigations should include routine haematobiochemistry and a computed tomography (CT) brain scan with contrast enhancement.
- If the CT scan does not reveal a structural lesion she should be considered for a temporal artery biopsy.
- If it is positive or if symptoms are persuasive corticosteroids should continue; a suggested regimen in Box 2.108. Bone protection is essential.

Discussion

How is GCA diagnosed and treated?

The British Society for Rheumatology and British Health Professionals in Rheumatology has produced guidelines (summarised in Box 2.108) for the diagnosis and management of GCA. Most treatment recommendations are based on expert opinion.

Which tests might help confirm a diagnosis of GCA?

Ninety-five per cent of patients with GCA have raised inflammatory markers, notably an erythrocyte sedimentation rate (ESR) > 40 or plasma viscosity > 1.8 or C-reactive protein (CRP) > 10; the CRP is less likely to be raised because GCA does not involve a vigorous T-helper-1-mediated immune acute-phase reaction. Thrombocytosis, normochromic–normocytic anaemia and hypoalbuminaemia are common in GCA.

Temporal artery biopsy is positive in around 70–80% of cases of GCA (especially if biopsies more than 2 cm long are taken to avoid missing skip lesions) but there is uncertainty about how long after starting corticosteroids a biopsy might be useful. The most popular view is that changes might disappear within 3–7 days, but some experts feel that histopathological legacies of GCA can remain for a long time afterwards.

^{18}F-labelled fludeoxyglucose positron emission tomography (FDG-PET) scanning may aid diagnosis of GCA, in which there is 'lighting-up' of the cranium, but atheroma can produce similar appearances.

What is the place of steroid-sparing agents in GCA?

Methotexate or azathioprine may be used if corticosteroids are contraindicated, or if it is not possible to wean successfully from steroids. They are sometimes used as steroid-sparing agents. They take 3 or 4 months to reach full effect and should never be used acutely. Methotrexate is started at 2.5 mg once weekly, increased to 5 mg, then to 7.5–10 mg once weekly long term. However, many patients following GCA or polymyalgia rheumatica (PMR) feel less well when off steroids and this is often not because of reactivation of GCA or PMR; partial hypoadrenalism from adrenal suppression may be the culprit.

In which patients is azathioprine dangerous?

Azathioprine can cause bone marrow suppression, more likely in those with genetically lower levels of thiopurine methyltransferase, which should be checked before initiating treatment.

What is PMR?

PMR is a common inflammatory disease in older people. The pathology of PMR is still unclear, unlike GCA with which PMR can be associated, but there are increased concentrations of T-helper-type-1 (interleukin-1 and interleukin-6) and type-2 (interleukin-10)-driven cytokines in affected tissues.

How is PMR diagnosed and treated?

The British Society for Rheumatology and British Health Professionals in Rheumatology has produced guidelines (summarised in Box 2.109) for the diagnosis and management of PMR. The cardinal features of PMR – proximal pain and stiffness with a raised acute-phase response – are straightforward enough but unhelpfully proximal pain and stiffness are not exclusive to PMR, a third of patients have systemic symptoms such as weight loss and a fair proportion may have distal musculoskeletal features including peripheral arthritis and oedema. Moreover, raised inflammatory markers occur in a wide range of infections (including bilateral septic arthritis), neoplasia and inflammatory diseases. Tenderness is not present in PMR, more likely in a myositis. PMR is also associated with GCA in 10% of its cases and up to 50% of cases of GCA may have polymyalgic symptoms. Response to steroids is widely used as a defining feature of PMR. The dose of 15 mg is sufficient to melt PMR symptoms away within 2 or 3 days whilst a higher dose will suppress symptoms of a diverse array of pathology, and in typical cases at least a 70% improvement in symptoms is expected.

Box 2.108 **Summary of diagnosis and management of giant cell arteritis (GCA)**

Early recognition and diagnosis

GCA should be considered in patients > 50 years presenting with the symptoms listed in Table 2.115, with particular attention to the predictive features of jaw claudication, diplopia and temporal artery abnormalities.

Confirmation of diagnosis – temporal artery biopsy

Temporal artery biopsy (TAB) should be considered whenever GCA is suspected but should not delay prompt institution of high-dose glucocorticosteroid therapy. Biopsy specimens should be no less than 1 cm, ideally greater than 2 cm, in length. Contralateral biopsy is usually not required. Patients with negative TAB but a typical clinical picture and response to steroids should be regarded as having GCA. Imaging techniques do not replace TAB for diagnosis of cranial GCA but may be important to exclude intracranial causes of symptoms.

Large-vessel GCA

Large-vessel GCA should be suspected in patients with prominent systemic symptoms, limb claudication or persistently high inflammatory markers despite adequate glucocorticosteroid therapy. Imaging techniques, such as positron emission tomography and magnetic resonance imaging scanning, should be reserved for the assessment of suspected large-vessel involvement.

Initial corticosteroid therapy

High-dose glucocorticosteroid therapy should be initiated immediately when clinical suspicion of GCA is raised. In uncomplicated GCA (no jaw / tongue claudication or visual symptoms) oral prednisolone 40–60 mg (not less than 0.75 mg / kg) should be used daily until resolution of symptoms and laboratory abnormalities. In complicated GCA (evolving visual loss or history of amaurosis fugax) intravenous methylprednisolone 500 mg to 1 g daily for 3 days should be administered before prednisolone. For established vision loss at least 60 mg prednisolone daily is needed. Bone and gastrointestinal protection should be considered.

Corticosteroid reduction

Steroid reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease, balanced against the need to use the lowest effective dose, patient wishes and side effects. The standard regimen is 40–60 mg prednisolone (not less than 0.75 mg / kg) continued for 4 weeks (or until resolution of symptoms and laboratory abnormalities), reduced by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2–4 weeks to 10 mg, and then by 1 mg every 1–2 months, provided there is no relapse. Some patients may benefit from a more gradual reduction, or a period of treatment at a stable dose, such as 5 mg for 3 months.

Low-dose aspirin

This should be considered in all patients with GCA, if there are no contraindications.

Monitoring of therapy

Patients should be monitored for evidence of relapse, and disease-related and steroid-related complications. Monitoring should be clinical, supported by measurement of inflammatory markers. In particular the following features should be sought: headaches, jaw and tongue claudication, visual symptoms, vascular claudication of limbs, bruits and asymmetrical pulses, polymyalgic symptoms, osteoporotic risk factors and fractures, or other corticosteroid-related complications, other symptoms that may suggest an alternative diagnosis. Frequency of follow-up is advised as: weeks 0, 1, 3, 6 then months 3, 6, 9, 12 in the first year (extra visits if relapse or adverse events). At each visit a full blood count, inflammatory markers, urea and electrolytes and glucose should be obtained, and every 2 years a chest radiograph to monitor for aortic aneurysm (echocardiography, magnetic resonance imaging or positron emission tomography may also be appropriate). Bone mineral density measurement is important.

Relapse

Disease relapse should be suspected in patients with a return of symptoms of GCA, ischaemic complications, or unexplained constitutional or polymyalgic symptoms. Relapse is usually associated with a rise in erythrocyte sedimentation rate / C-reactive protein, but may occur with normal inflammatory markers. For headache only, treatment is the previous higher steroid dose. For headache and jaw claudication, treatment is 40–60 mg daily prednisolone. For eye symptoms treatment is either 60 mg prednisolone or intravenous methylprednisolone. For large-vessel GCA investigation with imaging techniques (magnetic resonance imaging or positron emission tomography) and treatment should be considered using systemic vasculitis protocols.

Recurrent relapse

Recurrent relapse or failure to wean corticosteroids requires consideration of adjuvant therapy, such as methotrexate or other immunosuppressants. These immunosuppressive agents should be started at the third relapse.

Box 2.109 **Summary of diagnosis and management of polymyalgia rheumatica (PMR)**

Diagnostic approach

A stepped diagnostic process for the evaluation of PMR comprises assessment for core inclusion and core exclusion features, exclusion of mimicking conditions, assessment of the response to a standardised dose of 15 mg prednisolone and confirmation of diagnosis at early follow-up.

Core inclusion features are:

- Bilateral shoulder and / or pelvic pain
- Morning stiffness > 45 minutes
- Abrupt onset
- Age > 50 years
- Duration > 2 weeks
- Acute inflammatory response.

Box 2.109 **Summary of diagnosis and management of polymyalgia rheumatica (PMR)—cont'd**

Core exclusion features are:

- Active cancer
- Infection
- Giant cell arteritis (GCA)
- Other inflammatory conditions, e.g. rheumatoid arthritis, other connective tissue diseases
- Other non-inflammatory conditions, e.g. osteoarthritis, other local joint pathology
- Endocrine diseases, e.g. thyroid disease
- Drug related, e.g. statin myopathy.

Investigations

Appropriate investigations should be performed prior to corticosteroid commencement, including full blood count, urea and electrolytes, liver function, calcium, inflammatory markers (erythrocyte sedimentation rate/plasma viscosity or C-reactive protein), thyroid function, creatine kinase, autoimmune profile if relevant, and chest X-ray.

Specialist referral

This should be considered for atypical clinical presentation:

- Age < 60 years
- Chronic onset
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- 'Red flags', e.g. prominent systemic features, weight loss, night pain or neurological signs
- Peripheral arthritis or other features of autoimmune or muscle disease
- Normal or very high inflammatory markers.

Or treatment dilemmas:

- Incomplete or non-response to corticosteroids
- Ill-sustained response to corticosteroids
- Inability to reduce corticosteroid dose
- Need for prolonged corticosteroid therapy (> 2 years)
- Contraindications to corticosteroids.

Corticosteroid therapy

A suggested initial oral steroid and tapering regimen is prednisolone 15 mg daily for 3 weeks, then 12.5 mg daily for 3 weeks, then 10 mg daily for 4–6 weeks, then reduction by 1 mg every 4–8 weeks, or alternate day reductions (e.g. 7.5 mg / 10 mg alternate days). Intramuscular methylprednisolone may be used in milder cases and may reduce the risk of steroid-related complications (initial dose 120 mg every 3–4 weeks, reducing by 20 mg every 2–3 months). But treatment must be flexible and tailored to the patient and patient wishes, disease activity and steroid toxicity.

The duration of steroid therapy is usually 1–3 years, although some require small doses beyond. Steroids may be stopped if there is continuing lack of inflammatory symptoms. Raised inflammatory markers without clinical symptoms are not an indication to continue.

In the absence of GCA, urgent steroid therapy is not indicated before complete clinical evaluation.

Bone and stomach protection should be co-prescribed with corticosteroids.

Monitoring and follow-up

Early follow-up is necessary at 1–3 weeks post steroid commencement with a follow-up schedule of weeks 0, 1–3, 6 and months 3, 6, 9, 12 in the first year (extra visits if relapses or adverse events). Clinical monitoring at each visit should include consideration of disease activity and response to treatment, complications of disease (including GCA and large-vessel vasculitis), steroid-related side effects, atypical features or alternative pathology, and persistent pain (may arise from degenerative or soft-tissue pathology such as rotator cuff tears). Laboratory monitoring at each visit should include full blood count, inflammatory markers, urea and electrolytes and glucose or urine dipstick.

Relapse

Relapse is the recurrence of PMR symptoms or the onset of GCA, not just unexplained raised inflammatory markers. For clinical features of GCA treatment is as for GCA. For clinical features of PMR prednisolone should be increased to the previous higher dose or a single dose of intramuscular methylprednisolone 120 mg given. Adjuvant immunosuppressive therapy may be considered after two relapses.

CASE 2.48 PYREXIA AND SEPSIS

Candidate information

Role

You are a doctor on the acute medical unit. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

Dear Doctor

Re: Dr John Watson, aged 60 years

Thank you for admitting this 60-year-old ex-hospital ophthalmologist who is now engaged in regular overseas aid work. He presents with pyrexia of unknown origin. He has had night sweats and fever for the past few months. He has a documented temperature of 38°C. He has lost 2 kg in weight. He is usually well, although was briefly an inpatient in your hospital 3 months ago for incision and drainage of a staphylococcal abscess in his groin, when he was incidentally noted to have microcytic anaemia, with a haemoglobin of 10.5 g/dl. A subsequent ferritin was borderline low but his other haematinics were normal. He is awaiting outpatient endoscopies. I wondered if he had a soft systolic murmur, not previously documented, but examination is currently unremarkable. His blood tests reveal a C-reactive protein of 156 and his white cell count is mildly elevated.

Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Dr John Watson is a 60-year-old ex-hospital ophthalmologist with a month or so of fever, drenching night sweats and weight loss of around 2–3 kg. He has had occasional blood in his urine for around 2 months. He is usually well but 3 months ago developed an abscess in his groin, which required a short hospital admission to the surgical wards for incision and drainage. While in hospital he was found to be anaemic, and is awaiting outpatient endoscopies to exclude a source of covert bleeding. He has no symptoms of indigestion, change in bowel habit or family history of colorectal cancer. He has had a cough for the last few months, but it is mild and he had not thought much of it. His other past history is removal of a skin melanoma 5 years ago, thought to be completely excised. He does not take any medications. He is now semi-retired but does intermittent overseas medical work, largely cataract surgery. Six months ago he was in Africa, where he did not take adequate anti-malarial prophylaxis because the tablets made him feel sick, but was well on return. Nevertheless, he feels he could still be at risk from malaria, and is a little concerned about the possibility of human immunodeficiency virus (HIV) having sustained occasional minor needlestick injuries overseas. He has never smoked. He is married with two children, and all are well at home although there has been a 'throat bug' in the family.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Consider the causes of pyrexia.** Fever is a state of elevated core temperature above 38°C, often part of the defensive resistance to invasion of live (micro-organisms) or inanimate matter recognised as pathogenic or alien by the host. The term 'pyrexia' is often used synonymously with fever. Fever should be distinguished from hyperthermia, an unregulated rise in body temperature due to a failure of temperature homeostasis. The classic definition of pyrexia of unknown origin (PUO) or fever of unknown origin (FUO) is a febrile illness of at least 3 weeks' duration, with repeated temperature measurements of 38.3°C or higher, that defies diagnosis after 1 week of hospital inpatient evaluation. This has subsequently been modified to remove the requirement that investigations be inpatient. Unfortunately, many clinicians use the term PUO loosely to include any fever for which a cause has not been found, which should be discouraged because the most likely causes of short-term fevers are different from those of PUO. He therefore may have PUO, although strictly his temperature has not been documented and there are numerous potential causes that could be rapidly confirmed or excluded by tests. A full history should be taken of the nature of symptoms and their chronology, thinking of potential causes (Table 2.116).

There are many potential causes of PUO so it is not possible to list a standard battery of tests for every case, and it is preferable to tailor investigations according to clues from history and repeated examinations.

Infections in immunocompromised people (transplant recipients, HIV-infected patients, neutropenic patients) can present in an atypical fashion, as can infections in patients taking antipyretics, corticosteroids or antibiotics. It has been suggested that PUO can be subclassified into four different types – classic, nosocomial, immune-deficient and HIV-related.

Causes vary geographically and demographically. In developing countries PUO is more frequently due to infections. The relative likelihood of PUO being due to specific causes is related to age. In children, infections are the most common cause. Haematological malignancies and solid tumours are more common causes in elderly patients than in younger adults. Infections and connective tissue disorders are also frequent causes in the elderly, and giant cell arteritis and polymyalgia rheumatica are particularly common. Bacterial endocarditis is now a less common cause because it can now be diagnosed relatively quickly.

Patient perspective

His thoughts are entirely reasonable.

Past medical history

The recent staphylococcal abscess must be considered as a potential source of sepsis, perhaps with secondary subacute bacterial endocarditis, although staphylococcal endocarditis is invariably acute and aggressive. The history of melanoma cannot be ignored.

Drug and allergy history

It is unlikely that this is relevant in this case.

Table 2.116 Causes of pyrexia of unknown origin

Category	Causes / examples		Possible clinical clues
Infection (30%)	Localised bacterial (+ / – pyogenic)	Intra-abdominal: Subphrenic, diverticular, hepatic abscess Biliary sepsis	Abdominal pain
		Osteomyelitis, e.g. vertebral	Prostheses
		Septic arthritis	Exquisitely tender joint
		Skin and soft-tissue infection	History of oedema or eczema Intravenous drug abuse (lemon juice and the practice of licking needles dissolves drugs but is a perfect culture medium for serious organisms); necrotising fasciitis and deep tissue infections such as psoas abscesses (causing pain on leg straightening and the 'bent-knee' sign) are now common
		Dental abscess	Tenderness of a tooth
		Sinusitis	Tenderness of facial sinuses or mastoid
		Chronic otitis media	Otalgia Conductive hearing loss
		Unresolving pneumonia	Chest symptoms
		Unresolving urinary tract infection	Frequency Dysuria Loin pain
		Genitourinary infection	Vaginal or urethral discharge Dysuria, Dyspareunia Pelvic pain
		Brain abscess	Headache, focal neurological signs
		Tuberculous meningitis	Confusion
	Systemic bacterial	Rheumatic fever	Streptococcal throat infections
		Infective endocarditis	Prosthetic valve or native valve disease Invasive (including dental) procedures
		Salmonellosis / typhoid	Gastroenteritis
		Atypical pneumonia, e.g. *Coxiella* infection, psittacosis	Usually very unwell Contact with animals
		Brucellosis	Unpasteurised milk
		Leptospirosis	Occupational history (sewers)
		Listeriosis	Dairy products, soft cheeses, etc.
		Lyme disease (sometimes also *Bartonella* infection)	Tick bite
		Tuberculosis	Cough Night sweats Weight loss
		Syphilis	Index of suspicion
	Viral	HIV infection	Lymphadenopathy Recurrent fungal / viral infections
		Hepatitis B or C	Risk factors
		Epstein–Barr virus	Sore throat

Table 2.116 Causes of pyrexia of unknown origin—cont'd

Category	Causes / examples		Possible clinical clues
	Fungal	Systemic candidiasis	Usually immunocompromised
		Cryptococcal meningitis	Known HIV infection
	Protozoal	Malaria	Travel to malaria zone
		Giardiasis	Common
		Amoebiasis	Swimming in infected water
		Toxoplasmosis	Pet cat
	Worm	Toxocariasis	Pet dog
Neoplasm (15–20%)	Lymphoproliferative disease		Night sweats Lymphadenopathy Splenomegaly
	Renal cell carcinoma		Lack of early warning symptoms Classic triad of flank pain (40%), haematuria (40%) and flank mass (25%) rare; 25–30% discovered as incidental finding Weight loss and night sweats Hypertension Varicocoele Paraneoplastic – hypercalcaemia (PTHrp), polycythaemia (EPO), iron deficiency anaemia, non-metastatic liver dysfunction, neuromyopathy
	Lung cancer		Cough, haemoptysis, weight loss, smoker
	Hepatocellular carcinoma		Complication of cirrhosis
	Colorectal cancer		Especially elderly
	Carcinomatous meningitis		Headache, confusion
	Metastatic disease		Symptoms of primary, e.g. gastrointestinal, lung, breast, prostate, skin
	Atrial myxoma		Very high ESR
Inflammatory disease – autoimmune / connective tissue (15–20%)	Systemic vasculitides		Renal impairment Haemoptysis or respiratory symptoms
	Rheumatoid arthritis		Arthritis
	Lupus		Skin rashes Arthralgia
	Polymyositis		Muscle tenderness
	Adult Still's disease		Arthralgia, fever, rash, raised white cell count, sore throat, lymphadenopathy, abnormal liver function, negative serology
	Giant cell arteritis		Headache Visual disturbance Jaw pain
	Sarcoid meningitis		Confusion
Miscellaneous and unknown	Deep vein thrombosis or pulmonary thromboembolism		Tachypnoea
	Drugs / toxins		Antibiotics, NSAIDs, AEDs
	Periodic fever syndromes		Family history

AED, anti-epileptic drug; EPO, erythropoietin; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug; PTHrp, parathyroid hormone-related peptide.

Family history

A family history of colorectal or renal cancer should be explored.

Social history

His occupational history with overseas travel is potentially highly relevant, exposing him to malaria and needlestick injuries. A history of exposure to animals including household pets and farm animals is part of routine enquiry for PUO, as is a history of insect bites, including tick bites, a food history (poorly cooked meat, etc.), a history of unwell contacts, a sexual history and enquiry about intravenous drug taking.

SUMMARY BOX – ASSESSMENT AND PLAN

- The differential diagnosis remains wide without further tests but possible infectious causes include staphylococcal bacteraemia (with endocarditis essential to exclude after his recent abscess and a possible new heart murmur), malaria and tuberculosis. Malignant causes include renal cell carcinoma and metastatic melanoma.
- Routine blood tests include full blood count, urea, electrolytes and creatinine, liver function tests, calcium, erythrocyte sedimentation rate, C-reactive protein and multiple blood cultures from separate sites. Blood film examination for malarial parasites should be performed. A range of blood serology testing for viruses and autoantibodies may be indicated in a true pyrexia of unknown origin.
- Urinalysis for blood is essential, and if present should be analysed for casts.
- A chest X-ray and echocardiogram are important early tests.
- Further tests are almost inevitable, but dictated by the preliminary information. A contrast-enhanced computed tomography scan of chest, abdomen and pelvis would be important to look for metastatic disease or carcinoma, and differentiates between cystic and solid masses.
- Empirical antibiotics, steroids or antipyretics usually thwart successful investigation and should be avoided if possible.

Discussion

What causes pyrexia?

The release of certain cytokines and acute-phase reactants involved in the immune response.

What is sepsis?

This refers to systemic illness caused by microbial invasion of parts of the body that are normally sterile. The term septicaemia is old-fashioned and encompasses the better terms:

- Infection
- Systemic inflammatory response syndrome (SIRS), which may be due to sepsis, characterised by a temperature > 38°C or < 36° C, tachycardia > 90 beats/min, a respiratory rate > 20 breaths/min and a white cell count > 12 000/mm^3 or < 400/mm^3; it may also occur in trauma, burns and acute pancreatitis
- Sepsis (inflammation with evidence or suspicion of a microbial cause)
- Severe sepsis (sepsis with organ dysfunction – renal, respiratory, hepatic, haematological, central nervous system, cardiovascular – leading to lactic acidosis, renal impairment, acute lung injury, liver dysfunction, thrombocytopenia, confusion and cardiac dysfunction)
- Septic shock (a subset of severe sepsis with hypotension despite volume replacement).

Severe sepsis and septic shock have mortality rates of 25–30% and 40–70%, respectively, partly because early phases may not be recognised as sepsis or vigorously treated.

What host factors may predispose to sepsis?

Host factors that affect susceptibility to sepsis include immune status, illness severity, damage to tissues and indwelling lines.

How do bacteria induce sepsis and septic shock?

Lipopolysaccharide-binding protein on host cells (e.g. monocytes) binds to lipopolysaccharide on Gram-negative bacteria and transfers it to CD14, which resides on the host cell membrane. Cellular activation requires CD14 and a co-receptor known as a Toll-like receptor (TLR-4 for lipopolysaccharide). Gram-positive bacteria may induce similar pathways via other TLRs (TLR-2, TLR-6, TLR-9) or by producing exotoxins that act as superantigens or by directly stimulating immune cells via their proteins; superantigens are molecules that bind to major histocompatibility complex class II molecules of antigen-presenting cells and T-cell receptors activating large numbers of T cells and inciting a powerful pro-inflammatory response. All cases of septic shock involve overt pro-inflammatory responses, often with initial monocyte release of mediators (e.g. tumour necrosis factor-α (TNF-α), interleukins (ILs), platelet-activating factor, prostaglandins) provoking neutrophil activation and T-helper-1 lymphocyte-mediated inflammation, with vasodilatation and intravascular coagulopathy, and organ damage.

What are some important clinical and laboratory markers of sepsis and its associated inflammation?

Important clinical markers may include fever (or hypothermia), tachycardia, tachypnoea, hypotension, confusion, oliguria, positive fluid balance and hypoxia.

Easily accessible laboratory markers may include leucocytosis, elevated C-reactive protein, hyperglycaemia, elevated creatinine, elevated plasma bilirubin, thrombocytopenia and elevated international normalised ratio. Lactate is invariably elevated.

The pro-inflammatory response provoked after the initial recognition of lipopolysaccharides is complex, and it is increasingly understood that genetic factors often determine susceptibility or protection by the severity of this response. Many markers of this response are recognised, but few are yet clinically available.

What are early warning scoring systems?

These are systems used to identify serious illness, notably sepsis, early, using scoring charts with parameters such as heart rate, blood pressure, respiratory rate, temperature, conscious level and urine output.

What are the general approaches to managing sepsis?

Questions that should always be posed include: What is the likely organism? Where might it have come from? Why has this patient got it? Where else might the infection have gone? What is the likely resistance profile? Managing sepsis requires early recognition, supportive care, source control, antibiotics (the earlier the better) and specific non-antibiotic adjuvant therapies. Adjuvant therapies have achieved increasing prominence in severe sepsis, since mortality is 30–60% even with all other measures in place. These include:

- Early goal-directed therapy, which refers to early protocols in emergency departments designed to achieve early physiological stability before transfer to an intensive care unit, in such parameters as central venous pressure, mean arterial pressure and urine output; it refers to doing all basic things well such as timely use of fluids and blood transfusion and ionotropes and evidence is compelling
- Corticosteroids (many patients in intensive care have adrenal insufficiency though there is no value in synacthen testing as results are chaotic)
- Safe but not tight glycaemic control
- Consideration of recombinant human activated protein C, recommended in adults with severe sepsis with two or more major organs involved in the setting of optimum intensive care support but not effective in adults with severe sepsis but at low risk of death (acute physiology and chronic health evaluation (APACHE) < 25 or single organ failure) since APC is a natural anticoagulant and increases the rate of serious bleeding
- Gastric protection against stress ulceration
- Venous thromboembolism prophylaxis.

Staphylococcus is commonly detected in blood cultures. Which factors alert you to its reflecting true bacteraemia rather than being a ‘contaminant’?

These include the presence of local or systemic signs of infection, detection of bacteria in both culture bottles, a time to blood culture positivity less than 14 hours, coagulase-negative *Staphylococcus* (although not always the case!) and previous colonisation with staphylococci.

What types of disease can *Staphylococcus aureus* cause?

S. aureus is a versatile pathogen carrying significant morbidity and mortality. Infection is usually endogenous in origin, with approximately one-quarter of the population carrying one or more strains, principally in the nose. It can cause a broad spectrum of disease from mild skin and soft-tissue infections (SSTIs) to severe life-threatening bacteraemic disease.

S. aureus is a leading cause of community- and hospital-acquired bacteraemia, and rates have risen with increased use of intravascular catheters. The overall mortality of 20–40% has remained largely unchanged over several decades. Complications of bacteraemia include infective endocarditis and metastatic seeding to almost any body site. Bones, joints, meninges and prosthetic devices are particularly prone to metastatic seeding of *S. aureus* following bacteraemia. In adults, haematogenous *S. aureus* osteomyelitis most often involves the vertebral bodies. Patients over the age of 50 with community-acquired bacteraemia and no identifiable primary focus are at highest risk. The joint synovium is highly vascular and susceptible to haematogenous infection. Septic arthritis usually involves a single joint but may be polyarticular in people with rheumatoid arthritis (RA). Patients with immunosuppression and/or RA are at particular risk.

Host risk factors for complications include community acquisition of bacteraemia, absence of identifiable infective focus, presence of an indwelling foreign body and comorbidities such as malignancy and HIV. Complications are often occult and it is impractical to investigate all *S. aureus* bacteraemia extensively, but factors that predict complications developing (by no means robust) include a time to blood culture positivity less than 14 hours, positive follow-up blood cultures 48–96 hours after the first positive blood culture result, persistent fever 72 hours after initial positive blood culture result, skin findings suggestive of an acute systemic infection and a new murmur.

The pathogenicity of *S. aureus* is also related to a large number of virulence factors that include bacterial components such as surface-associated molecules. *S. aureus* also produces a number of secreted products, including superantigens, cytotoxins such as Panton–Valentine leucocidin (PVL), and secreted enzymes.

What is toxic shock syndrome?

Toxic shock syndrome is an acute, potentially fatal condition characterised by temperature $> 38.9\,°C$, rash and desquamation (especially palms and soles), hypotension and multi-system involvement. Toxic shock syndrome often develops from a site of colonisation and is related to the production of exotoxins. The proportion of cases related to menstruation has dropped and non-menstrual cases may be associated with localised infections, surgery or insect bites.

What do you know about 'MRSA'?

This is meticillin-resistant (but more appropriately multi-resistant) *S. aureus* because of its multi-resistant cassette gene; β-lactamase production was one of the traditional modes of antibiotic resistance, followed by production of antibiotics that inhibited β-lactamase. MRSA simply changed its target to become resistant again. In the early 1990s MRSA was a rare problem; now all doctors must be conscious of MRSA. Historically, Gram-negative organisms were the main cause of sepsis, then in the 1990s the high emergence of MRSA put Gram-positives in the limelight; with better control of MRSA in recent years Gram-negative and fungal organisms are seeing new-found predominance.

Risk factors for MRSA colonisation

These include recent hospitalisation, recent (3–6 months) antimicrobial use, invasive lines (intravenous, urinary catheters), recent surgery, nursing home residence, advanced age, underlying severe disease, exposure to a colonised or infected patient, morbid obesity and orthopaedic implant surgery.

Indications for MRSA eradication treatment

Clinical indications are stronger than treatment for those with colonisation. Isolated nasal carriage has a reasonable chance of clearance, but skin carriage and colonisation of indwelling catheters cannot be cleared.

Staff screening for MRSA carriage

This was popular, but it is apparent that many staff can have negative skin carriage at the start of a shift and be positive by the end of a shift.

Patient screening for MRSA carriage

Eighty-five per cent of carriage of MRSA is asymptomatic, but these people have a much higher risk of clinical infection when unwell; 15% of people have clinical infection. Same-day polymerase chain reaction testing has improved detection, and is used increasingly in at-risk patients.

MRSA prevalence control

Handwashing and prudent use of antibiotics (e.g. avoidance of quinolones which select MRSA) are imperative.

What do you know about community-associated *S. aureus*?

MRSA is classically acquired during contact with healthcare institutions and is known as hospital-associated MRSA (HA-MRSA). However, community-associated MRSA (CA-MRSA) is an increasing problem and CA-MRSA strains are different, often susceptible to a wider range of antibiotics, and resemble community strains of meticillin-sensitive *S. aureus* (MSSA). Most of them produce the PVL toxin.

What do you know about PVL *S. aureus*?

PVL toxin is encoded by a mobile phage that produces two gene products that assemble with each other to form a membrane-perforating complex that destroys white blood cells and causes tissue necrosis. PVL-related disease is often associated with severe infections including necrotising pneumonia, usually in healthy young adults, often with a history of recurrent 'boils'. Currently in the UK, PVL-related disease is mostly associated with MSSA, with small clusters of MRSA. It is rapidly increasing in prevalence. Risk factors for acquiring PVL *S. aureus* are the five 'C's:

- Contaminated items
- Close contact, such as with contact sports
- Crowding, such as in households, gyms, prisons and military training camps
- Cleanliness (lack thereof)
- Cuts and other compromised skin integrity.

Clinical features suggestive of PVL *S. aureus* are given in Box 2.110.

Box 2.110 **Clinical features of Panton–Valentine leucocidin (PVL) *Staphylococcus aureus* disease**

Skin and soft-tissue infections (often recurrent and may occur in clusters)

- Furunculosis, carbuncles, folliculitis, cellulitis
- Cutaneous lesions > 5 cm
- Pain and erythema out of proportion to severity of skin findings
- Necrosis

Invasive infections (may occur in young, immunocompetent host)

- Necrotising, cavitating pneumonia (suspect with respiratory symptoms and sepsis following a flu-like illness, haemoptysis, hypotension, marked leucopenia, very high inflammatory markers, raised creatine kinase or numerous staphylococci on Gram film of sputum); the CURB-65 (confusion, urea, respiratory rate, blood pressure) score can underestimate the severity of this condition with a mortality of around 75%
- Necrotising fasciitis
- Osteomyelitis, septic arthritis and pyomyositis
- Purpura fulminans
- Cardiac abscesses

Swabs from infected skin or nares may reveal the presence of PVL-positive *S. aureus*.

Neither flucloxacillin nor vancomycin will stop toxin production, and clindamycin and linezolid are often used, although it is the toxin, rather than ongoing infection, which gives rise to the high mortality.

What do you know about vancomycin intermediately and fully resistant *S. aureus* (VISA)?

VISA does not reliably respond to glycopeptides and is not detected by routine microbiological methods. The mechanism of resistance is probably related to a thicker capsule. VISA should be suspected in any patient who has persistent *S. aureus* infection despite prolonged glycopeptide treatment.

What are the treatments for staphylococcal infection?

Most SSTIs can be dealt with in the community using oral antibiotics. Severe disease requires parenteral antibiotics.

- Flucloxacillin is the treatment of choice for MSSA infection and parenteral glycopeptides are preferred for MRSA in most situations.
- Other antibiotics include rifampicin, fusidic acid, clindamycin (very effective for staphylococcal and streptococcal SSTIs but resistance rapidly occurs during treatment and *Clostridium difficile* may occur) and tetracyclines.
- Other treatments for MRSA and other severe *S. aureus* infections include: glycopeptides (vancomycin, teicoplanin) – glycopeptide-resistant *S. aureus* has occurred, the gene jumping from *Enterococcus*; linezolid (a novel, bacteriostatic oxazolidinone antibiotic which inhibits MRSA toxicity, useful for vancomycin-resistant *Enterococcus*, usually reserved for severe SSTI or pneumonia, but may cause bone marrow suppression or peripheral and optic neuropathy); daptomycin (a bactericidal lipopeptide for severe SSTIs but not respiratory infections as it is inhibited by secretions); and tigecycline (a glycylcyclin, structurally related to tetracyclines, with broad-spectrum activity, for treatment of complicated SSTIs and complicated abdominal infections caused by multiple-antibacterial-resistant organisms).
- Combination therapy with agents such as clindamycin and linezolid are needed to suppress PVL and alpha-toxin production, with rifampicin for intracellular clearance of staphylococci. Intravenous immunoglobulins may be considered because of their action in neutralising exotoxins and superantigens.

How is resistance to antibiotics tackled?

Health-care-associated infection is now a very serious issue.

Resistance to infection is common but not necessary. Some countries, such as the Netherlands, have very low rates of it; for example the rate of MRSA here is around 25–50-fold less than in the UK.

Resistant infections include *C. difficule*, MRSA, vancomycin-resistant *Enterococcus*, extended spectrum beta-lactamase *Klebsiella pneumoniae*, multi-resistant *Acinetobacter baumannii*, coagulase-negative staphylococci, *Legionella pneumophila*, viral hepatitis and HIV infection, and emerging infections that could become resistant include *Acinetobacter*.

The prudent use of antibiotics is essential. Resistance occurs because resistant organisms are selected by antibiotics that kill other harmless or protective bacteria and allow resistant, nefarious ones to flourish. Antibiotics should be started only with good cause or indication, using small-spectrum agents where possible, and stopping these if it becomes apparent that infection is not present. Where infection is confirmed, the regimen should be modified if microbiological results dictate so. Dosages should be correct and not so low as to create selection of resistant organisms. The shortest duration of treatment possible should be used.

Prevention of transmission or cross-infection is very important, requiring personal and hand hygiene, aseptic approaches, the use of devices only with strict indication and removal of unnecessary devices; this requires always questioning why a device is *in situ*.

Surveillance and action includes isolation of infected patients, the use of gloves and gowns and sometimes masks, and involvement of the infection-control team.

What tropical diseases should acute physicians be aware of?

Malaria

Malaria is one of the most common imported infections, increasing in prevalence in the UK with an increasing travelling population, and the threat of warming European climates alluring mosquitoes.

The five species are: *Plasmodium falciparum* (common in sub-Saharan Africa and Papua New Guinea), *Plasmodium vivax* (Central and South America, North Afrcia, Middle East, Indian subcontinent), *Plasmodium ovale* (West Africa), *Plasmodium malariae* (Africa) and *Plasmodium knowlesi* (South East Asia).

Clinical features are produced from asexual forms in the blood which destroy red cells, localise in organs, obstruct the micro-circulation and release toxins leading to the classical rigors and fevers. The incubation period ranges from 7 days to many years, but *P. falciparum* generally less than 6 weeks. After a period of fatigue and non-specific symptoms, abrupt fever develops with hot, cold and sweat phases; the periodicity with *P. falciparum* is variable.

Features of severe malaria (caused by *P. falciparum*) include cerebral malaria (encephalopathy and coma), respiratory failure (pulmonary oedema), hypoglycaemia, shock, acidosis, bleeding, renal involvement and blackwater fever and severe anaemia.

Diagnosis definitively is made by thick and thin blood film examination.

Treatments for non-falciparum malaria include chloroquine and primaquine. Treatments for falciparum malaria include quinine, doxycycline, clindamycin, Malarone, Riamet and Lariam for mild malaria, and artesunate, quinine and quinidine for severe malaria. There can be extensive side effects.

Dengue

Dengue fever is a common mosquito-borne arboviral infection seen in many parts of the world such as the Far East. There are four types, none conferring immunity against another. It typically produces high fevers with raised inflammatory markers, and often tachycardia or hypotension, in the context of a patient looking surprisingly well. The dangerous effects are dengue shock syndrome and dengue haemorrhagic shock syndrome, the latter less common than the former, either occurring generally with a second or subsequent infected strain. Shock syndrome is usually successfully treated with fluid resuscitation until it passes (if in hospital), whilst haemorrhagic shock syndrome has a higher mortality rate even with intensive care. Shock syndromes tend to occur days or weeks into the illness at the time fever is settling, and so the most risky time is when patients look well enough for discharge from hospital; they should not be!

Diarrhoeal diseases

Acute watery diarrhoeal diseases include viral diseases (rotavirus, norovirus, adenovirus, cytomegalovirus), bacterial diseases (enterotoxigenic *Escherichia coli*, *Vibrio cholera*, *Aeromonas hydrophila*, *Salmonella enterica*, *Shigella* spp., *Campylobacter jejuni*) and protozoal diseases (*Cryptosporidium* spp., *Giardia intestinalis*, *Cyclospora cayetanensis*).

Acute bloody diarrhoeal diseases include bacterial diseases (*Shigella* spp., enterohaemorrhagic *E. coli*, enteroinvasive *E. coli*), protozoal diseases (*Entamoeba histolytica*, *Balantidium coli*) and helminths (*Schistosoma mansoni*).

Persistent diarrhoeal diseases include enteropathogenic *E. coli*, enteroadherent *E. coli*, *Mycobacterium tuberculosis*, *Cryptosporidium* spp., *G. intestinalis*, *Isospora belli*, microsporidia and *Strongyloides stercoralis*, conditions also common in immunosuppressed people.

Leishmaniasis

Leishmania protozoal parasites are transmitted by phlebotomus sandfly, and though the condition is uncommon in the UK it affects 1.5–2 million people per year worldwide.

Visceral leishmaniasis is common in India, the Sudan and the Mediterranean basin. It causes chronic fever, splenomegaly and pancytopenia, sometimes with hepatomegaly, lymphadenopathy, hypoalbuminaemia and hypergammaglobulinaemia. Symptoms are less obvious in immunosuppressed people, and visceral leishmaniasis in HIV is a major problem worldwide. Diagnosis is by direct visualisation of parasites on microscopy (the best tissues being bone marrow or splenic), although direct agglutination and dipstick tests are fairly sensitive. Treatments include amphotericin.

Cutaneous leishmaniasis occurs in Africa, the Middle East and Central Asia (Old World cutaneous leishmaniasis species) and South and Central Aemrica (New World cutaneous leishmaniasis species). It presents with one or more nodules on exposed areas (hands or face) that enlarge and ulcerate over weeks, after an incubation period of usually months. Diagnosis is by direct visualisation of parasites on microscopy, or polymerase chain reaction testing. Mucocutaenous leishmaniasis occurs in South America and causes nasal stuffiness, bleeding, ulceration and septal perforation from mucosal inflammation. Treatments for cutaneous leishmaniasis and mucocutaenous leishmaniasis include sodium stiboglucanate.

Schistosomiasis

Schistosomiasis is a predominantly African trematode (fluke) helminth disease whose intermediate host is an aquatic snail as it cannot complete its life cycle in humans. Free swimming cercariae invade skin or mucous membranes, develop into schistosomula, and migrate via the circulation to mesenteric or vesical veins. *Schistosoma haematobium* lives in the bladder venous plexus and deposits eggs in the bladder mucosa. *Schistosoma mansoni* lives in the mesenteric and portal veins and deposits eggs in the bowel mucosa. Symptoms include haematuria and haematospermia, and acute manifestations due to ectopic worm migration include neurological schistosomiasis. Diagnosis is supported by history and eosinophil count. Treatment is with praziquantel, sometimes preceded by corticosteroids.

What do you know about renal cell carcinoma?

This constitutes 2–3% of all adult malignancies, is twice as common in men, and usually presents in the fourth to sixth decades.

The cause is usually unknown. Smoking doubles the risk, and it is associated with obesity, unopposed oestrogen, hypertension, petroleum products, heavy metals, tuberose sclerosis and acquired cystic kidney disease or chronic kidney disease, dialysis and immunosuppression (relative risk × 80). It also occurs in rare hereditary syndromes such as von Hippel–Lindau (autosomal dominant, 3p deletion, multiple cancers).

It usually arises in the proximal tubule epithelium and histologically may be clear cell 75% (proximal tubule origin, 3p deletion), chromophobic, chromophilic, oncocytic or of collecting duct type.

Renal cell carcinoma is often an incidental finding. Haematuria, a flank mass or loin tenderness may occur, but symptoms may equally be the result of cytokines such as erythropoietin or IL-6. Renal cell carcinoma is a great mimicker. It can produce a raised haemoglobin or iron deficiency anaemia (a cytokine inhibits iron incorporation into the haem synthetic pathway), thrombocytosis or leucocytosis including eosinophilia (the tumour releases

IL-5). Thirty-five per cent of renal cell carcinoma presents with metastases, most commonly lung, but sometimes soft tissue, bone, liver, skin or central nervous system. Symptoms often improve after resection of the primary tumour.

The mode of treatment depends upon staging because the disease may be confined to the kidney or extend to perinephric fat, the renal vein and inferior vena cava, regional nodes, adjacent viscera including adrenals, or more distantly with distant metastases. Surgery is the only potentially curative treatment for localised tumour, by radical nephrectomy. Palliative nephrectomy may alleviate symptoms such as pain, hypercalcaemia and polycythaemia. Regression of metastases has been reported after nephrectomy but nephrectomy cannot be considered adjuvant treatment. The disease is relatively resistant to radiotherapy or chemotherapy but the former may palliate bone or cerebral involvement. Immunotherapy has shown promise.

What are periodic fever syndromes?

Periodic fever syndromes are founding members of a family of conditions known as autoinflammatory syndromes. Autoinflammation is explained in Box 2.111.

Periodic fever syndrome refers to a group of hereditary periodic fevers that may be autosomal dominant or recessive. These are listed in Table 2.117. The pathophysiology is complex and differs between disorders. IL-1β secretion depends on recognition of antigen and initial intracellular signalling by TLRs, the first structures of the innate immune system which recognise infective antigens or tissue damage, leading to production of pro-IL-1β. Pro-IL-1β is further processed by protein complexes containing MEFV (pyrin) and CISA1 (cryopyrin) genes. Additional 'danger signals' are usually required to activate these processing protein complexes to cleave pro-IL-1β into the mature cytokine. Mutated cryopyrin can self-activate cleavage of pro-IL-1β. Pyrin inhibits cleavage of pro-IL-1β and when mutated results in increased levels of IL-1β. Syndromes and their features of attacks are shown in Table 2.117. Inflammatory markers may be raised during attacks. Steroids and biological therapies may help symptoms.

Other hereditary autoinflammatory conditions include deficiency of interleukin-1 receptor antagonists, pyogenic sterile arthritis / pyoderma gangrenosum / acne and chronic recurrent multifocal osteomyelitis.

Box 2.111 **Autoinflammation and autoimmunity**

Autoinflammation occurs in numerous immunologically mediated conditions that arise by activation of the innate immune system.

This is in contrast to autoimmune conditions, which arise as a result of to aberrant adaptive immune responses involving antigen-specific T cells and B cells.

Table 2.117 Periodic fever syndromes

Disorder		Immunopathology	Features
(Familial) Mediterranean fever		Pyrin mutations leading to increased IL-1β	1–3-day attacks of lower-limb erythema, monoarthritis, sterile serositis (peritonitis, pleuritis, pericarditis), scrotal swelling Typically Mediterranean ancestry May present in adulthood
Hyperimmunoglobulinaemia D with periodic fever		MVK gene mutation, mechanism unclear	3–7-day attacks of erythema, arthralgia, occasional peritonitis, lymphadenopathy and splenomegaly Presents in childhood
Tumour necrosis factor-associated periodic fever syndrome		*TNFRSF1α* gene mutation, mechanism unclear, possibly impaired TNF-induced apoptosis or NF-κB signalling	7–21-day attacks of migratory rash overlying myalgia, peritonitis, pleuritis conjunctivitis and periorbital oedema
Cryopyrin-associated periodic fever syndrome	Familial cold autoinflammatory syndrome	Cryopyrin mutations leading to increased IL-1β	Varying degrees of urticarial rash, arthralgias, uveitis, aseptic meningitis and amyloid
	Muckle–Wells syndrome		
	Chronic infantile neurological, cutaneous and articular syndrome/neonatal onset multi-system inflammatory disease		
NLRP12-associated periodic syndrome (NAPS12)		Increased IL-1β	

IL, interleukin; TNF, tumour necrosis factor.

CASE 2.49 WEIGHT LOSS AND MALIGNANCY

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr George Ross, aged 86 years
>
> Thank you for reviewing this gentleman, who was admitted to hospital last year with anaemia while staying with relatives. He was apparently transfused and on his return I referred him to the hospital here for further investigation. Unfortunately his appointment was superseded by a family bereavement and he missed it. He did, however, see a rheumatologist on account of joint pains and shoulder discomfort who felt the overall position to be anaemia of chronic autoimmune disease. He has been on steroids, with some improvement initially, for 6 months. But he has now become more unwell again, tired and, significantly, losing weight. On examination I did wonder about a mass in the right iliac fossa. He has type 2 diabetes and his blood glucose has risen to around 20. I wonder if you have any further advice on diagnosis and management.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr George Ross is an 86-year-old man who has become tired and has lost around 10 kg in weight over the last 6 months. His clothes have become extremely loose. He and his wife went to stay with their daughter and son-in-law in Scotland last year; during their visit, Mr Ross became 'unwell' (a little light-headed and confused) and was admitted to hospital. There he was treated for a urinary tract infection and noted to be anaemic and was transfused with blood. Referral for investigation of his anaemia was interrupted when his brother died in London and family support was needed there. Mr Ross did see a rheumatologist, having also been troubled with joint pains, who felt he might have 'rheumatoid or polymyalgia'. He denies any history of proximal girdle pain or morning stiffness. Mr Ross also has type 2 diabetes and takes metformin and simvastatin, but is on no other medications. He has no other symptoms. He was a very active and well-maintained man until last year, playing golf most days.

Box 2.112 **Causes of weight loss**

- Malignancy – gastrointestinal or non-gastrointestinal
- Chronic disease, e.g. heart failure, chronic obstructive pulmonary disease
- Chronic infection
- Non-infectious inflammatory disease, e.g. vasculitis
- Neurodegenerative conditions
- Thyrotoxicosis
- Late-onset type 1 diabetes
- Undernutrition
- Depression

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

■ **Select the important presenting symptoms.** This case very typically highlights the sort of presentation seen in elderly care. There is more than one thing going on, and it is important to keep an open mind about previous opinions and focus on what are important and potentially threatening symptoms now. These are undoubtedly tiredness (likely to be the result of anaemia) and weight loss.

■ **Take a thorough systematic enquiry for causes of weight loss (Box 2.112).** Take a full systematic enquiry but pay particular attention to:

- Gastrointestinal symptoms – abdominal pain, nausea and vomiting, altered bowel habit (diarrhoea, constipation), gastrointestinal bleeding
- Steatorrhoea – type 2 diabetes is occasionally the result of pancreatic infiltration
- Prostatic symptoms – difficulty getting started, thin stream, nocturia, incomplete emptying, frequency
- Adrenal insufficiency symptoms – dizziness, nausea and vomiting.

■ **Decide what to do with less urgent symptoms and problems.** The joint symptoms might be less pressing than the abdominal mass and weight loss.

Patient perspective

Establish if he has had any thoughts about what his symptoms might represent.

Past medical history

There are no clues here.

Drug and allergy history

High-dose corticosteroids can mask symptoms of a wide range of diseases including cancer. Metformin is of course anorexogenic.

Family history

Ask about a family history of colorectal cancer.

Social history

As well as checking his alcohol and smoking history, aim to discover how his life has changed in the last few months, what he cannot do now that he could, any difficulties that might be posed by investigation (given recent family circumstances) and how he and his wife are currently managing.

SUMMARY BOX – ASSESSMENT AND PLAN

- The anaemia warrants further investigation to exclude malignancy. The weight loss is the most worrying feature. The right iliac fossa mass could represent constipation, but a full examination including per rectal examination is imperative.
- The history of autoimmune disease is uncertain and needs clarification from the case notes, but polymyalgia does not seem likely.
- Repeat full haematobiochemistry is warranted, including blood count, haematinics and inflammatory markers, and a chest X-ray.
- Urgent investigation of the lower gastrointestinal tract is warranted first, with either colonoscopy or computed tomography scanning. The latter may be preferable and faster to organise in patients who are frail and may show disseminated disease.
- Metformin should be stopped in this anorexogenic situation, and perhaps substituted with a sulphonylurea.
- Bone protection should be instituted early for patients taking long-term corticosteroids (but is a lesser issue immediately and the aim here is likely to wean the steroids).

Discussion

Is the C-reactive protein (CRP) usually raised in cancer?

Inflammatory markers are often normal, and if elevated seldom very high, especially CRP (CRP often under 50); the plasma viscosity or erythrocyte sedimentation rate may be elevated significantly in certain cancers such as renal cell cancer and some lymphoproliferative states, and in metastatic disease, but low or normal levels should not provoke false reassurance.

What are the commonest malignancies?

Leading cancers worldwide in approximate order of frequency are lung, stomach, breast, colorectal, prostate, liver, oropharyngeal, gynaecological, oesophageal, leukaemia and bladder.

How might you approach the problem of cancer of unknown primary (CUP) site?

CUP accounts for 3–9% of patients, and issues raised include whether or not to investigate, the primary site involved, the histological type, which investigations to consider, the prognostic implications of these investigations and possible treatments.

Presenting sites

The most common sites of presentation (excluding head and neck), with decreasing prevalence, are lymph nodes, bone, liver and other abdominal sites, lung and pleura, central nervous system, skin and adrenals. Identification of the primary site (as well as the histology and degree of spread) is central to management but needs to be tailored to the patient's likely prognosis and prospects for treatment.

Whether or not to investigate?

Exhaustive investigation of poor performance status patients is often counterproductive because of the diminishing likelihood of identifying a primary site, the increasing expense of continuing investigation and discomfort incurred with limited life expectancy. Even after postmortem examination the primary site may remain unknown.

Primary sites – likelihood

Primary sites, in order of decreasing likelihood, are lung, pancreas, colorectal, renal, liver, gastric, prostate, ovary, thyroid, adrenal, breast and parotid.

Histological types

Adenocarcinoma is the most common histological type (over 50%). Next are poorly differentiated tumours, and minorities include squamous carcinoma, lymphoma, germ cell tumours, melanoma, sarcoma and neuroendocrine tumours. Squamous CUP usually presents with cervical lymphadenopathy, or rarely inguinal lymphadenopathy of disease originating in the anus, vulva or penis.

Investigations to localise the primary site

A panel of histochemical and genetic markers may help identify likely primary sites including thyroid transcription factor-1 for lung cancer, CK7 and CK20 cytokeratins and CdX to differentiate between gastrointestinal, gynaecological and breast origin, oestrogen receptor and progesterone receptor for breast and endometrium and prostate specific antigen for prostate. Serum tumour markers are of low specificity and do not contribute to diagnosis.

Computed tomography (CT) has traditionally proved to be the most successful technique for identifying the primary site in patients presenting with adenocarcinoma of unknown origin. Magnetic resonance imaging (MRI) is advantageous in the pelvis and in identifying occult breast cancers. Fludeoxyglucose positron emission tomography (FDG-PET) and PET-CT to detect occult primary carcinomas outside the head and neck region may be useful (24–71% sensitivity), better, for example, for lung than some tumours. The most frequent primary diagnoses following investigation are non-small-cell lung cancer and pancreatic cancer and not those with the greatest treatment potential. Breast, ovary and prostate are the more treatable origins of adenocarcinoma of unknown primary (ACUP). A primary breast cancer may be found in 40–70% of women presenting with isolated axillary lymph node metastases. MRI is a valuable adjunct to mammography and ultrasound. For most patients presenting with bone metastases, investigation with CT scan of chest, abdomen and pelvis is likely to reveal a primary source in the lung (24%), prostate (17%) or breast or gynaecological organs (16%).

Prognostic factors

The overall median survival for all patients with CUP varies from 12 to 22 weeks, a better prognosis defined by disease in limited nodal sites or a single site of metastasis, performance status 0–2, weight loss less than 10% and absence of liver metastases on CT.

Patients commonly present with liver metastases. Chemotherapy directed at tumours of gastrointestinal origin can result in a median survival of 7 months, depending upon performance status and serum lactate dehydrogenase levels. Specific chemotherapy regimens even for these traditionally less treatable cancers and other adenocarcinomas of the gastrointestinal tract that present as CUP can give good palliation for 6–12 months. Multiple small-volume lung metastases due to thyroid carcinoma are rare, but response to treatment with radioiodine can often be achieved. Patients with central nervous system disease from CUP have a poor prognosis.

Possible treatments

Poorly differentiated cancers can be the most treatable, and chemotherapy curable. A distinctive subgroup of patients with poorly differentiated or ACUP have characteristics that differ from patients with well-differentiated adenocarcinoma – a younger age, rapid progression of symptoms (< 30 days) and tumour growth, and tumour expression of germ cell markers α-fetoprotein or human chorionic gonadotrophin; lymph nodes within the mediastinum and retroperitoneum are often more infiltrated. This subgroup may include a high proportion of germ cell tumours that may be more responsive to chemotherapy and potentially curable.

Most malignant lymph node masses in the neck are metastatic, arising from primary head and neck tumours (squamous carcinoma of cervical or supraclavicular nodes), although primary lung cancer should be suspected when the lower cervical or supraclavicular lymph nodes are involved. The prognosis here has improved with modern surgery and chemoradiotherapy.

The management of patients presenting with lymphadenopathy due to metastatic melanoma is primarily surgical. They should be staged by PET-CT scan if the disease is clinically confined to a resectable nodal basin in order to exclude distant metastases. The prognosis following lymphadenectomy can be excellent, with 55–58% 5-year survival. The management of isolated deposits of metastatic melanoma in other sites such as lung is also primarily surgical.

If after all efforts the primary site has not been identified, palliative chemotherapy treatment with combination chemotherapy such as carboplatin, gemcitabine and capecitabine can achieve responses in 20–40% of selected patients.

How would you approach the problem of febrile neutropenia?

Bone marrow suppression is usually the limiting factor of cytotoxic chemotherapy. Drug-induced DNA damage in bone marrow progenitor cells causes falls in neutrophil counts, and patients with neutropenia are at increased risk of sepsis. The timing of neutropenia is predictable; it typically lasts over a 7–14-day period with the nadir usually around day 10, but all patients should be considered to be at risk of sepsis if they have received chemotherapy within the past 28 days. The risk correlates with both the absolute neutrophil count and the duration of neutropenia: a low nadir ($< 500/\text{mm}^3$) and protracted duration (> 10 days) are major risk factors.

Defining febrile neutropenia

Febrile neutropenia refers to a single oral temperature of 38.3°C or above, or 38°C or above for 1 hour or longer, and a neutrophil count of $500/\text{mm}^3$ or less, or a count below $1000/\text{mm}^3$ and predicted to fall below $500/\text{mm}^3$ within 24–48 hours. Any chemotherapy patient presenting with a sustained fever (≥ 37.5°C) and low neutrophil count ($< 1000/\text{mm}^3$) should be treated as potentially septic.

Common organisms

These are Gram-positives (mostly) including *Staphylococcus* spp., *Streptococcus pneumoniae*, *Streptococcus viridans*, *Enterococcus faecalis* and *Corynebacterium* spp., Gram-negatives including *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa* and anaerobes including *Bacteroides* and *Clostridium* spp.

Clinical features

Symptoms and signs of inflammation are frequently absent and patients typically present with fever in the absence of focal signs. Fever may be absent if patients are also taking steroids. The primary sites of infection are often mucosal (mouth or gut), or at sites of vascular access.

Management

Blood cultures and empirical broad-spectrum antibiotics are warranted immediately. Afebrile neutropenic patients with symptoms or signs of infection should be managed identically. Initial intravenous therapy regimens vary – monotherapy with a broad-spectrum penicillin (piperacillin/tazobactam), third- or fourth-generation cephalosporin or penem are reasonable, and there is no clear advantage of combination therapy in most uncomplicated episodes. Glycopeptide therapy (vancomycin) may be important in cases with catheter-associated infection or mucosal injury but resistant enterococci limit its use to specific indications and not as empirical first-line therapy. The single most important determinant of discontinuation of antibiotics is neutrophil recovery. Colony-stimulating factors (granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor) stimulate neutrophil precursor recovery and can shorten the duration of neutropenia but there is no clear evidence that adding these agents to empirical antibiotics provides significant benefit although they may have a role in protracted neutropenia where the risk of secondary fungal infection is high, and in patients receiving potentially curative chemotherapy who have experienced a previous episode of severe febrile neutropenia. Prophylactic antibiotics to prevent infection remain contentious.

What are the non-myelosuppressive complications of chemotherapy?

Non-myelosuppressive complications of cancer therapies (specific targeted therapies as well as conventional cytotoxics) include the following.

Hypersensitivity and acute drug reactions

Mild hypersensitivity reactions without hypotension or bronchospasm are managed by stopping the drug, hydrocortisone and chlorpheniramine. More severe anaphylactic reactions require intensive management. Paclitaxel is notorious for hypersensitivity, requiring routine premedication and dexamethasone prophylaxis. Irinotecan provokes an acute cholinergic syndrome with sweating, diarrhoea, tachycardia and palpitations. Oxaliplatin can provoke an acute neuropathy.

Extravasation

Attempts should be made to aspirate back an extravasated drug. Ice packs should be applied and steroid creams reduce inflammation. Dexrazoxane is used to treat extravasation.

Tumour lysis syndrome

Tumour lysis syndrome is a well-recognised complication of treatment of acute leukaemia and high-grade lymphoma, and less commonly solid tumours. It provokes characteristic metabolic derangements – hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia – as a consequence of rapid and massive lysis of tumours. These cause muscle weakness, cramps, paraesthesiae, paralysis and arrhythmias. Hyperuricaemia and hyperphosphataemia cause renal failure owing to urate and calcium phosphate crystal formation. Tumour lysis syndrome is treated with high fluid loads. Allopurinol inhibits xanthine oxidase conversion of xanthene to urate and is used where there has been no allopurinol prophylaxis. Rasburicase is a recombinant urate oxidase that converts uric acid into allantoin, which is excreted, and is considered in established tumour lysis syndrome. Haemodialysis may be required. Hypocalcaemia should be corrected only if symptomatic, to prevent worsening calcium phosphate deposition.

Emesis

If emesis is uncontrolled and oral intake inadequate, intravenous fluid and electrolytes are needed. Highly emetogenic regimens require pre-medication with high-dose steroids and 5-hydroxytryptamine 3 (5-HT3) antagonists, with follow-on oral steroids and oral anti-emetics such as domperidone or 5-HT3 antagonists. The NK-1 inhibitor apprepitant or longer acting 5-HT3 antagonists such as palenosetron should be considered for refractory symptoms.

Gastrointestinal toxicity

Gastrointestinal toxicity is second only to bone marrow toxicity. The mechanism is similar throughout the gastrointestinal tract, but symptoms depend on the site of damage. Oral mucositis or stomatitis commences about 5–10 days after starting chemotherapy, with erythema followed by ulceration and secondary infection, usually with candidiasis. Dysphagia, dyspepsia and nausea are common. Mucositis is a complex process of epithelial and submucosal DNA damage, rapid cell death, and activation of multiple cascades mediated through generation of reactive oxygen species. Treatment includes antiseptic and analgesic midbrain, and topical and systemic antifungals or antibiotics. Parenteral hydration or nutrition is occasionally required. Keratinocyte growth factor-1, a member of the fibroblast growth factor family, is a recombinant therapeutic agent that significantly reduces severe mucositis when used prophylactically in patients undergoing stem cell transplants. Diarrhoea is the commonest lower gastrointestinal complication, and treatment is usually supportive. Secondary infection can prolong it.

Cardiotoxicity

Anthracyclines are cardiotoxic (dilated cardiomyopathy), inducing direct and cumulative myocardial damage, but greater understanding of dose thresholds for cardiotoxicity and modern, less cardiotoxic anthracyclines have reduced this problem. Trastuzumab is a monoclonal antibody targeting the cell surface signalling molecule HER-2, which is overexpressed in some breast and other cancers; HER-2 is also important in cardiac development and in the response to cardiac injury and trastuzumab is cardiotoxic in a minority of patients. Tyrosine kinase inhibitors treat a wide range of cancers; lapatinib, an inhibitor of both HER-1 and HER-2, seems relatively safe but others that target various oncogenic signalling pathways may induce QTc prolongation.

Renal toxicity

Cisplatin is notoriously nephrotoxic, and high fluid intake is required.

Skin toxicity

A non-specific dermatitis is very common with chemotherapy. Palmar–plantar erythrodysaesthesia or hand–foot syndrome is common; it is due to interference with epidermal growth factor receptor (EGFR) function, characterised by palmoplantar erythema which can progress to painful desquamation. Skin toxicity associated with agents that interfere with EGFR function appears as an acneform rash predominantly affecting the trunk and face; agents such as cetuximab (a monoclonal anti-EGFR antibody), erlotinib and lapatinib (inhibitors of the intracellular tyrosine kinase activation region of EGFR) may provoke it.

What do you know about tumour angiogeneis in cancer and what strategies may be used to suppress it?

New blood vessel formation (angiogenesis) is a physiological process active in wound healing. It is tightly regulated by many pro- and anti-angiogenic factors. It is vital for cancer growth and metastasis, as tumours cannot grow beyond 200–300 μm in diameter unless they recruit new blood vessels to supply nutrients and oxygen.

Tumour angiogensis – why it occurs

Cancer cells promote a state of pro-angiogenic predominance. Hypoxia as tumour cells outgrow their available blood supply is one reason, with production of hypoxia-inducible factor-1 (HIF-1), which controls expression of several genes important in cellular adaptation to hypoxia including vascular endothelial growth factor (VEGF), endothelial growth factor and platelet-derived growth factor. Tumours with high EGFR expression include head and neck, renal cell, non-small-cell lung cancer, glioma, ovarian, pancreatic, colorectal, breast and gastric. Amplified signalling through phosphoinositide 3-kinase and its downstream target, mammalian target of rapamycin (mTOR), enhances HIF-1-dependent gene expression. Another reason for pro-angiogensis is changes in cell-to-cell interactions that occur in the highly proliferative state, augmented by the inflammatory and immune responses to cancer; further, specific clones of cancer cells with oncogenic mutations that stimulate production of pro-angiogenic factors or deletion of tumour suppressor genes that suppress angiogenesis are positively selected.

Tumour angiogenesis – molecular processes involved

VGEF-A is the prototype and most important member of the VEGF family of growth factors, which, together with their receptors, form one of the major pathways in tumour angiogenesis. In this family there are numerous individual growth factors (VEGF A–E and placental growth factors 1 and 2) and tyrosine kinase (TK) receptors (VEGFR 1–3, VEGFR 1 and 2 promoting angiogenesis and VEGFR 3 lymphangiogenesis). VEGF TK receptors (VEGFR) have an extracellular ligand-binding domain to which the growth factors attach with an intracellular TK part which activates protein kinase C downstream, thereby interacting with DNA in the nucleus. Neuropilin 1 and 2 are cell surface proteins that bind VEGF and may act as co-receptors. Other factors in angiogenesis and interacting with the VEGF pathway are fibroblast growth factor-2, which induces neovascularisation, platelet-derived growth factors (PDGF) expressed by activated endothelial cells, angiopoietin-1 and transforming growth factor α which impact on PDGF function and regulate endothelial integrity, and the Delta/Jagged–Notch system, one of whose ligands, Delta-like ligand 4 (DLL4), is strongly expressed in endothelial cells. New blood vessels predominantly sprout from established vasculature or intussusception when periendothelial cells divide an existing vessel into two. Tumour vessels tend to be tortuous, chaotic with poor lumen formation, and have structurally immature leaky walls with reduced cell coverage, their endothelial cells tend to be more dependent on VEGF for survival.

Treatments to suppress tumour angiogenesis

Endothelial cells that make up tumour vasculature are essentially 'normal' cells with a stable genome which reduces the chances of resistance to treatment. Anti-angiogenic agents specifically target the growth factors or proliferating endothelial cells without affecting other organs. One approach is blocking the pro-angiogenic pathways such as the VEGF pathway (antibodies to the ligand VEGF, the receptor, TK inhibitors, etc.). The antibody bevacizumab binds VEGF and is beneficial in recurrent colorectal, breast, non-small-cell lung, liver and renal cancer. VEGFR TK inhibitors include sorafenib and sunitinib. The impact of anti-angiogenesis is currently not profound, and this might reflect the large number of growth factors involved in the complex process of angiogenesis and bypassing of VEGF inhibition.

How might you diagnose and manage bone metastases?

Bone is an extremely common site of cancer metastases, and bone metastases are often painful. Hypercalcaemia and raised alkaline phosphatase levels can be a clue to diagnosis, but are not inevitable. Bone metastases can be detected on a bone scan (but myeloma, renal cell cancer and thyroid cancer characteristically producing lytic lesions that are missed), CT and MRI; plain X-ray films will show abnormalities only when at least half of the bone is involved, and pathological fracture and spinal cord compression should always be excluded. Treatment of metastatic bone pain may include analgesics, non-steroidal anti-inflammatory drugs, and bisphosphonates, systemic chemotherapy or hormonal therapy in some cases, and surgery in some cases. Radiation therapy, as a single fraction, half-body treatment or as a systemic radiopharmaceutical, can provide effective pain relief with minimal side effects.

CASE 2.50 TIREDNESS

Candidate information

Role

You are a doctor in the medical outpatient clinic. Please read the following letter from the patient's general practitioner (GP). You may make notes on the paper provided. When the bell sounds, enter the examination room to begin the consultation.

Scenario

> Dear Doctor
>
> Re: Mr Christopher Brandon, aged 42 years
> Thank you for seeing this gentleman with a history of tiredness and overall loss of energy for the last year. He has also been losing weight and feeling nauseated. He takes levothyroxine and his thyroid-stimulating hormone and free thyroxine suggest adequate replacement. Examination is unremarkable save for a slightly tanned complexion but he says he has always had this. His wife agrees. His full blood count, urea, creatinine, liver function tests and inflammatory markers are normal. His serum sodium is 121 mmol/l and his potassium is 5 mmol/l. His random blood glucose is on the low side at 3.5 mmol/l. Please see and advise on further management.
>
> Yours sincerely

Please take a history from the patient (you may continue to make notes if you wish on the paper provided). Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to take a history from the patient followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Be prepared to discuss solutions to the problems posed by the case and how you might reply to the GP's letter. You are not required to examine the patient.

Patient information

Mr Christopher Brandon is a 42-year-old man who has been feeling tired for around a year. He used to be very active, but since losing his teaching job a few years ago has found he has less energy, with a considerable decline in the last year. He now feels marked waning of energy and some dizziness on standing. He has lost a little weight but attributes this to nausea. He lives with his wife, is a lifelong non-smoker and seldom drinks alcohol. He has always tanned quickly, and is not sure if this has changed over the last year. He takes levothyroxine for an underactive thyroid but his tests indicate adequate dosage. He had a large operation for a maxillary sinus tumour 15 years ago followed by cranial radiotherapy, but was later told he was cured. Recently, his GP thought he might be depressed but he does not feel it. He and his wife would simply like to get back to 'doing things' again.

How to approach the case

Data gathering in the interview and interpretation and use of information gathered

Presenting problem(s) and symptom exploration

Patients may complain of feeling 'tired all the time', having 'no energy' or feeling 'exhausted'. It is important to try to establish:

- What is meant by tiredness (e.g. a general feeling of fatigue after minimal activity, or weakness in specific muscle groups)
- Whether symptoms are present all the time or are episodic. If episodic, do they occur at specific times of the day (e.g. rheumatoid arthritis causes morning stiffness that improves with activity while mechanical back pain may be worse towards the end of a working day) or after specific activities (e.g. myasthenia gravis causes fatiguable weakness in specific muscle groups)?
- The duration of symptoms
- The mode of onset of symptoms (insidious or sudden, following a specific illness?)
- Symptoms that might suggest a specific cause (Table 2.118).

Patient perspective

Establish if he has had any thoughts about what his symptoms might represent.

Past medical history

The history of pituitary radiation is potentially highly relevant.

Drug and allergy history

Levothyroxine is probably blameless here.

Family history

Relevance here is unlikely.

Social history

As well as checking his alcohol and smoking history aim to discover how his life has changed as a result of his symptoms, notably what he cannot do now that he could.

Discussion

What is chronic fatigue syndrome?

This typically follows an upper respiratory tract infection with incomplete recovery. Many viruses have been

Table 2.118 Symptoms that might suggest a cause of tiredness

Cause	Symptoms and clinical clues
Anaemia	Pallor Per rectal or vaginal bleeding Diet
Hypothyroidism	Preference for warmth Weight gain Dry skin and hair thinning
Obstructive sleep apnoea–hypopnoea syndrome	Snoring Obesity
Heart failure	Dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea Ankle swelling
Chronic lung disease	Dyspnoea
Inflammatory bowel disease	Altered bowel habit with blood, mucus or pus
Diabetes mellitus	Polyuria and polydipsia Recurrent fungal infections
Addison's disease	Postural dizziness Nausea Pigmented skin creases Vitiligo
Chronic kidney disease	Nocturia Oliguria
Colorectal cancer	Altered bowel habit Per rectal bleeding Weight loss
Lung cancer	Cough Haemoptysis Weight loss Smoking history
Myopathy/polymyalgia rheumatica	Persistent proximal muscle weakness
Myasthenia gravis	Fatigable weakness in certain muscle groups
Periodic paralysis (very rare)	Episodic marked generalised weakness
Depression	Depressed mood Loss of enjoyment, interest or pleasure in activities Diminished concentration Change in weight or appetite Sleep disturbance Suicidal ideation / attempts / specific plans Agitated behaviour or reduced activity
Chronic fatigue syndrome	Fatigue after minimal activity Antecedent viral illness
Iatrogenic, e.g. beta blockers	

SUMMARY BOX – ASSESSMENT AND PLAN

- The history and biochemistry suggest hypocortisolism.
- The question is whether this is primary hypoadrenalism or secondary to hypopituitarism.
- Primary hypoadrenalism, most commonly the result of Addison's disease, may result in a tanned complexion and hyperpigmentation of palmar creases and the buccal mucosa (adrenocorticotrophic hormone (ACTH) excess). It tends to be insidious but the history is usually months to a year or two before presentation. It may present as a crisis, or, frequently, with chronic symptoms without a crisis. Other causes of hypoadrenalism that should be considered include adrenal infiltration.
- Hypopituitarism is a common consequence of cranial irradiation. It can be much more insidious than Addison's disease, presenting many years, even decades, after initial damage to and subsequent atrophy of the pituitary gland. There may be pallor (loss of ACTH).
- He should have a synacthen test to confirm hypoadrenalism and if positive receive cortisol replacement (e.g. oral hydrocortisone). Large doses are unnecessary except in a patient presenting in an adrenal crisis. Imaging of the adrenal glands might identify a non-Addisonian cause. Pituitary disease may give rise to a positive synacthen test because of years of adrenal atrophy.
- ACTH levels can differentiate between primary hypoadrenalism (high) and hypopituitarism (low).
- Other tests to consider include a pituitary profile (thyroid-stimulating hormone, prolactin, insulin-like growth factor 1, follicle-stimulating hormone, testosterone) and magnetic resonance imaging (non-urgently).

implicated as possible causes. There are many possible symptoms, but profound fatigue, worsened by minimal physical or mental exertion, is central. Chronic fatigue syndrome is more common in females but there is no clear link with occupation or social class. Investigations are usually non-specific, although altered lymphocyte function, hypocortisolism and other altered blood parameters have been described in some patients. There may be full recovery, but symptoms may relapse and remit or persist as a chronic illness.

What is melatonin?

This is an important hormone in sleep–wake circadian rhythm regulation, produced in the pineal gland, ensuring we are awake in the daytime and sleep when it is dark. Melatonin levels increase at night and help induce deep, restorative sleep. Sleep changes occur with age and melatonin therapy is sometimes used in older people with primary insomnia. In all people disruption in getting up and going to bed times, even by an hour (not to mention shift-workers), can be dramatically disruptive to circadian regulatory hormones.

List some causes of hypoglycaemia

- Diabetic drugs
- Starvation

- Addison's disease
- Insulinoma

How might you approach the problem of medically unexplained symptoms?

The term medically unexplained symptoms is one we all understand, but which may carry false implication that a doctor has failed to diagnose. There are many other terms for a similar notion. Somatisation refers to the physical manifestation of a psychological disorder, and the term somatoform is sometimes used. Hysterical conversion disorder refers to loss of function, whilst the term functional disorder is an often codified, pejorative one. Hypochondriasis refers to severe and unjustified worry regarding disease, whilst malingering refers to the deliberate invention of signs. Functional imaging has been shown to prove this in rare cases, but malingering is an exceptionally pejorative term if misapplied without proof. The term psychologically determined or generated symptoms seems a more acceptable, accurate description for many patients.

Symptoms may be diverse, and may be overemphasised as is common with tingling, or underplayed as is common with weakness when patients might display remarkable 'la belle indifference' to their paralysed arm, or may be multiple and disparate and not add up to any reasonable single pathology.

Examples of possible psychologically involved disorders include fibromyalgia and irritable bowel syndrome, in which it seems likely that symptoms reflect a variety of processes including misperception of normal physiology.

It is commonly underappreciated by doctors that symptoms are merely perceptions, contributed to by a combination of pathology and beliefs. Indeed, the vast majority of symptoms cannot be fully explained by the scientifically biomedical model.

A thorough history is essential, as is appreciation of background attitudes, not just of the patient, but of the doctor. Antennae for mismatch or inconsistencies, for example pain being reported but a facial expression suggesting otherwise, exaggeration, falsification and markers of intentionality such as a limb failing before counterpressure is applied.

These patients should not be seen as time wasting, despite there sometimes seeming to be a sense of futility and a fear that investigation might reinforce or consolidate the patient's notion of disease. However, if investigation is undertaken, it should be packaged to a patient as very likely to exclude the very small possibility of disease.

Alternative medicine tends to focus on symptoms rather than underlying causes, which may be one reason why it appears to be effective where symptoms have more of a belief foundation than a pathological one. Some doctors, too, appear to have a gift of healing almost akin to hypnosis, which may reflect their intuition and ability to influence patient's beliefs and so assuage symptoms.

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Station 3

Cardiovascular and nervous system

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Cardiovascular system

Examination of the cardiovascular system

Inspection

Hands and arms

- Look for finger clubbing, characterised by fluctuant nail beds, loss of angle between the nail plate and posterior nail fold, and increased nail curvature. Cardiac causes include cyanotic heart disease and infective endocarditis.
- Look for cyanosis due to right-to-left cardiac shunts.
- Look for palmar or tendon xanthomata.
- Look for peripheral stigmata of infective endocarditis (Table 3.1).

Face and neck

- Look for central cyanosis at the tongue.
- Note any pallor or abnormal skin markings, specifically a malar flush. A malar flush may be a sign of pulmonary hypertension and you should especially consider mitral stenosis as a cause.
- Look for corneal arcus, a creamy yellow discoloration at the boundary of the iris and cornea caused by cholesterol deposition; it can be normal. Look for xanthelasmata.

Table 3.1 Peripheral signs of infective endocarditis

Sign	Appearance
Splinter haemorrhages	Multiple linear reddish-brown marks on the linear axis of nails (one or two may occur in healthy people)
Osler's nodes	Small painful, purplish nodules at the finger pulps representing digital microinfarction
Janeway lesions	Pink palmar macules
Roth's spots	Flame-shaped retinal haemorrhages with a cotton wool centre

Jugular venous pulse (JVP)

There are no valves between the right atrium and internal jugular vein, such that the degree of rise and distension of the JVP is dictated by right atrial pressure. The external jugular vein is superficial, prone to kinking in the fascial layers and thus not a guide to right atrial pressure. The right internal jugular vein is used in preference to the left. It runs a relatively straight course medial and deep to the sternomastoid, from between the sternal and clavicular heads to the angle of the jaw. It differs from the arterial pulse (Table 3.2) in numerous ways.

The JVP has a characteristic waveform (Table 3.3, Fig. 3.1).

Note that in relation to the electrocardiogram (ECG) the 'a' wave thus corresponds to a P wave and the 'x' descent to the QRS complex.

- Examine the JVP by positioning the patient at 45° and estimate the vertical height in centimetres between the top of the venous pulsation and the sternal angle to give the venous pressure in cm (Fig. 3.2). Normal is up to 3–4 cm.

Abnormal waveforms of the JVP are outlined in Table 3.4.

Table 3.2 Differences between jugular and carotid pulse

	Jugular	Carotid
Number of waveforms	Two: 'a' and 'v'	One
Upper level	Definite	Not defined
Shape of movement	Rapid inward	Rapid outward
Palpability	Impalpable	Palpable
Effect of respiration	Falls during inspiration (venous return increased by suction effect of lungs)	No effect
Effect of position	Varies	No effect
Effect of abdominal pressure	Rises	No effect

Table 3.3 Normal waveform of the jugular venous pressure

Waveform	When it occurs	What it represents
'a'	Presystolic	Venous distension due to right atrial contraction – blood, as well as entering the right ventricle, passes back through the open channel between the right atrium entrance and the jugular vein
'c' (a flicker in the x descent)	Ventricular systole	Closure of tricuspid valve whose leaflets bulge back towards the right atrium during ventricular systole
'x'	Synchronous with carotid pulse	Tricuspid valve drawing away from the right atrium as the right ventricle empties in systole (atrial relaxation also contributes to 'x')
'v'	*Not* synchronous with ventricular systole	Venous return to right atrium whilst tricuspid valve still closed
'y'	Precedes atrial contraction	Opening of tricuspid valve and blood rushing from the right atrium into the right ventricle just prior to 'kick' of atrial contraction

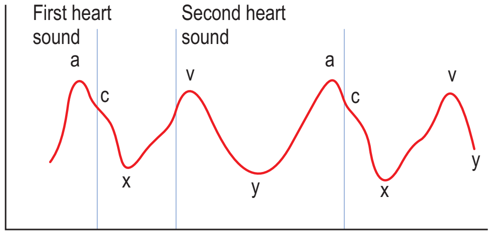


Figure 3.1 Normal waveforms of the jugular venous pulse.

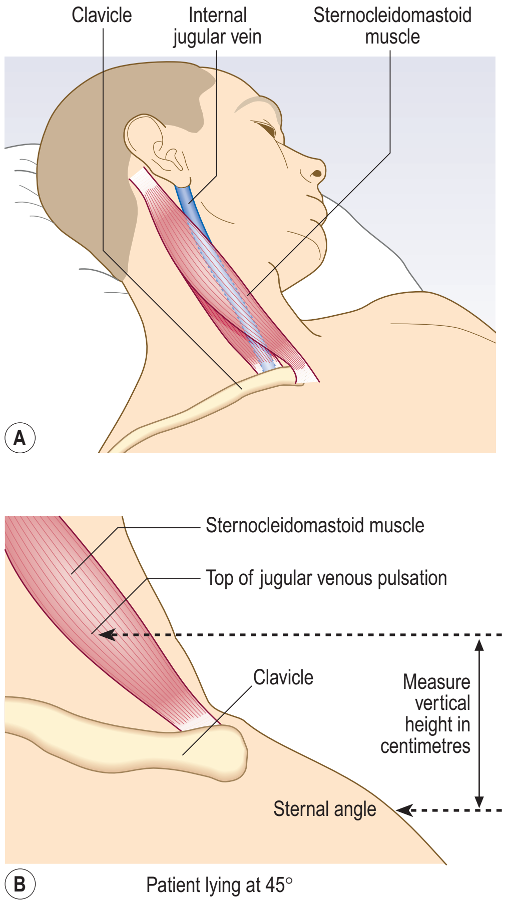

Clavicle
Internal jugular vein
Sternocleidomastoid muscle
A
Sternocleidomastoid muscle
Top of jugular venous pulsation
Clavicle
Measure vertical height in centimetres
Sternal angle
B
Patient lying at 45°

Figure 3.2 Measuring the jugular venous pulse.

Chest wall

- Look for a median sternotomy scar consistent with coronary artery bypass grafting, open mitral valvotomy or valve replacement, aortic valve surgery or mediastinal surgery.
- Look for a left lateral / inframammary thoracotomy scar consistent with closed mitral valvotomy.
- Look for the scar of (and palpable) a permanent pacemaker or implantable cardiac defibrillator.

Palpation

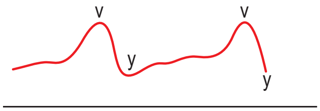
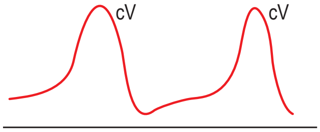
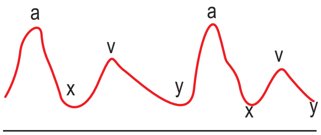
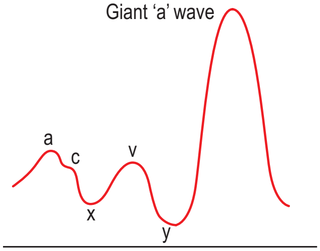
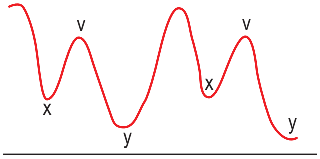
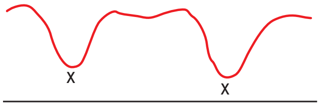
Arterial pulse

- Note the heart rate and rhythm.
- Palpate the radial or carotid pulse. Important abnormalities in arterial pulse character are shown in Table 3.5.

Blood pressure

- Take (or ask for) the blood pressure. Ensure you have the correct cuff size. Obese patients need a large cuff; a standard cuff will exert greater pressure to compress the artery and give falsely elevated readings. The point at which you hear the first

Table 3.4 Abnormal waveforms of the jugular venous pulse (JVP)

Abnormality		Causes	What it represents
Loss of 'a' wave		Atrial fibrillation	Loss of effective atrial contraction
Systolic V wave		Tricuspid regurgitation	'x' descent lost and replaced by very prominent upright systolic wave representing blood shooting back up into the neck as right ventricle contracts Synchronous with carotid pulse and called systolic 'V' wave (not to be confused with 'v' wave) Sometimes called 'cV' wave Frequently seen rising to the earlobes; 'y' descent steep as a result
Prominent 'a' wave		Tricuspid stenosis Pulmonary hypertension of any cause resulting in right ventricular overload Pulmonary stenosis	Atrium contracting against resistance; 'y' descent also slowed because ventricular filling impeded
Giant 'a' or cannon wave		Complete heart block	Atrium contracting against a closed ventricle
Kussmaul's sign		Pericardial constriction Also restrictive cardiomyopathy and severe right heart failure of any cause when venous pressures are high	Paradoxical rise in JVP on inspiration due to inability of right heart to accommodate blood volume of venous return without a marked rise in filling pressure; 'x' and 'y' descents correspondingly deep between the steep upstrokes
Raised venous pressure (> 4 cm)		Congestive biventricular cardiac failure Pericardial effusion Cardiac tamponade	In all of these arterial blood pressure may be low and in large effusions and tamponade apex beat absent. In tamponade only the 'x' descent is prominent Raised JVP + hypotension + absent apex beat = Beck's triad
Non-pulsatile (fixed) raised neck veins		Superior vena cava obstruction	Obstructed venous return at the level of the superior vena cava

Korotkoff sound is the systolic pressure and the point at which the sound disappears (fifth Korotkoff sound) is the diastolic pressure. The fourth Korotkoff sound (muffling) is acceptable in patients in whom sound does not disappear.

Be alert to a wide pulse pressure (aortic regurgitation) and a narrow pulse pressure (aortic stenosis). Be aware of the significance of differences in blood pressure between arms (leaking thoracic aneurysm) and greater than 15–20 mmHg between arms and legs, always palpat-

Table 3.5 Abnormalities in arterial pulse character

Pulse character	Causes	Description / what it represents
Normal		The percussion wave is the dominant wave transmitted along elastic arterial walls The dicrotic notch (difficult to detect) is a normal blip on the downstroke of the percussion wave representing aortic valve closure
Slow rising, plateau pulse ('anacrotic' pulse)	Aortic stenosis	Slow rising with delayed percussion wave and sometimes a palpable judder on the upstroke Characteristically associated with narrow pulse pressure (narrow difference between systolic and diastolic pressure) if severe
Collapsing pulse	Aortic regurgitation Arteriovenous fistula Patent ductus A large-volume, hyperkinetic pulse may occur in any cause of high cardiac output, e.g. thyrotoxicosis, Paget's disease, severe anaemia; a small-volume collapsing pulse (quickly rising but small percussion wave) is associated with ventricular run-off states, e.g. mitral regurgitation, ventricular septal defect	Very brisk upstroke followed by 'collapse' occurs when there is 'run-off' from the aorta Characteristically associated with wide pulse pressure (wide difference between systolic and diastolic blood pressure) if severe May be visible at brachials or carotids and best felt by raising the patient's arm, feeling the radial pulse 'slap' against your fingertips or palm
Pulsus alternans	Aortic stenosis Left ventricular failure	Alternating large and small beats A sign of poor left ventricular function
Pulsus paradoxus	Cardiac tamponade Pericardial constriction Acute severe asthma compromising venous return	Excessive fall in pulse pressure (> 10 mmHg) during inspiration Not, in fact, a paradox, but an exaggeration of normal physiology Difficult to detect
Jerky pulse	Hypertrophic cardiomyopathy	Ventricular ejection in 'stops and starts'

ing for radio-femoral delay otherwise silent aortic coarctation is missed.

Apex

- Aim to locate the apex beat with your middle finger, normally palpable in the fifth intercostal space at the mid-clavicular line, and determine if it is displaced (Fig. 3.3). An absent apex beat may be a sign of obesity, emphysema, pericardial effusion or dextrocardia, but it may be best palpable in the left lateral position. Many terms have been used to describe abnormalities in apex beat character (Box 3.1).

Right ventricular parasternal lift

- Also known as a right ventricular heave or a left parasternal heave, this is detected by placing your palm over the left lower parasternal edge (Fig. 3.3). It will palpably (and visibly) lift if there is right ventricular hypertrophy, itself usually a consequence of pulmonary hypertension of any cause.

Box 3.1 **Apex beat abnormalities**

- A *double impulse* may be a sign of hypertrophic cardiomyopathy.
- A *tapping apex* is the palpable equivalent of a loud first heart sound and should alert you to mitral stenosis.
- A *hyperdynamic* or *thrusting apex* should alert you to aortic regurgitation.
- A *sustained apex beat* should alert you to aortic stenosis.
- A *heaving apex* is a sign of left ventricular hypertrophy.

Apex beat abnormalities can be difficult. As a rule of thumb, try to determine whether the apex beat is displaced or undisplaced, and whether or not it is forceful.

Undisplaced apex

This is normal or implies pressure overload, as in aortic stenosis (raised left ventricular pressure with hypertrophy) and mitral stenosis (raised left atrial pressure with hypertrophy / dilatation).

Displaced apex

This implies volume overload, as in aortic regurgitation (left ventricular dilatation) and mitral regurgitation (left atrial and left ventricular dilatation).

Palpable heart sounds and murmurs ('thrills')

- Feel for any thrills. Thrills are palpable murmurs (like a purring lion cub) usually caused by blood being squeezed through a narrow aperture. They are the tactile manifestation of murmur energy. A systolic thrill at the apex suggests mitral regurgitation. An upper parasternal thrill suggests aortic stenosis (right parasternal edge) or pulmonary hypertension (left parasternal edge).

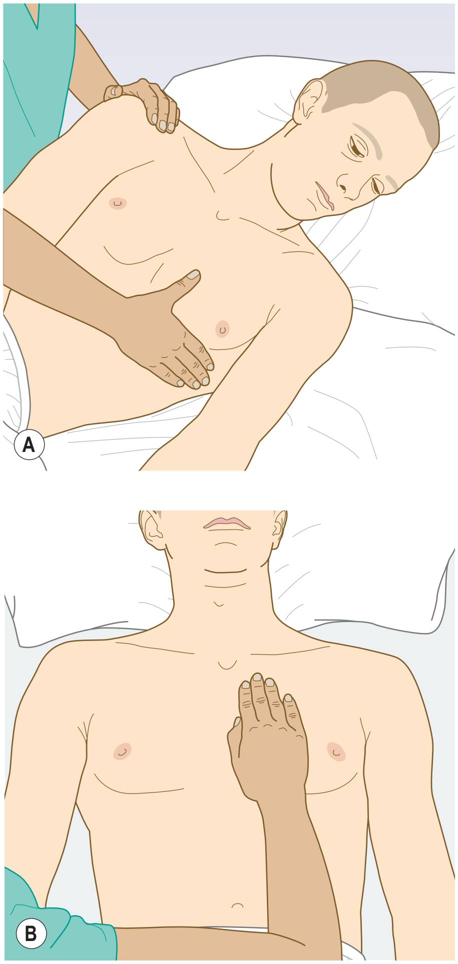


Figure 3.3 Determining the position of the apex beat (A) and palpating for a right ventricular heave (B).

Predicting valve abnormalities before auscultation

One of your aims in cardiovascular examination to this point should be to try to predict any valve abnormality before auscultation. Ideally, auscultation should confirm already aroused suspicions. Common examples are given in Table 3.6.

Percussion

Percussion of the cardiac border or cardiac dullness adds little to clinical assessment. Omit unless other signs suggest the presence of a pericardial effusion.

Auscultation

Auscultation sites

- Start at the apex with the diaphragm followed by the bell of your stethoscope, then move through the areas shown in Figure 3.4 with the diaphragm. The bell is a resonating chamber that amplifies low-pitched sounds, such as the diastolic murmur of mitral stenosis or a third or fourth heart sound. If not applied lightly it becomes a diaphragm.
- Next listen at the *apex* with the patient in the *left lateral position* and at the *aortic and pulmonary areas* with the *patient sitting forward*. Which you do first depends upon where you think the pathology lies, but be seen to do both. *In both positions listen in expiration ('breathe in, and out, and hold your breath… and breathe again') and in inspiration if you suspect a right-sided (pulmonary or tricuspid) murmur.* Inspiration increases the loudness of right-sided murmurs and expiration the loudness of left-sided murmurs.

Heart sounds

Heart sounds are vibrations caused by closure of heart valves combined with rapid changes in blood flow and tensing within cardiac structures.

Table 3.6 Predicting valve abormalities before auscultation

Pulse character	Pulse pressure	Apex position	Diagnosis
Normal (may be atrial fibrillation)	Normal	Undisplaced	Mitral stenosis (or normal!)
Large volume	Wide	Displaced	Aortic regurgitation
Small volume	Narrow	Undisplaced	Aortic stenosis
Normal	Wide / normal	Displaced	Mitral regurgitation

- Listen for the first and second heart sounds, and any extra third or fourth heart sound.

■ **First heart sound (S1).** S1 ('*lub*') represents mitral (and to a lesser extend tricuspid) valve closure at the onset of ventricular systole. Only one sound is audible. The intensity of S1 may be altered (Table 3.7) by the position of the mitral valve leaflets at the onset of systole, the rate of rise of the left ventricular pressure pulse, the amount of tissue, fluid or air between valve and stethoscope, and mitral valve disease.

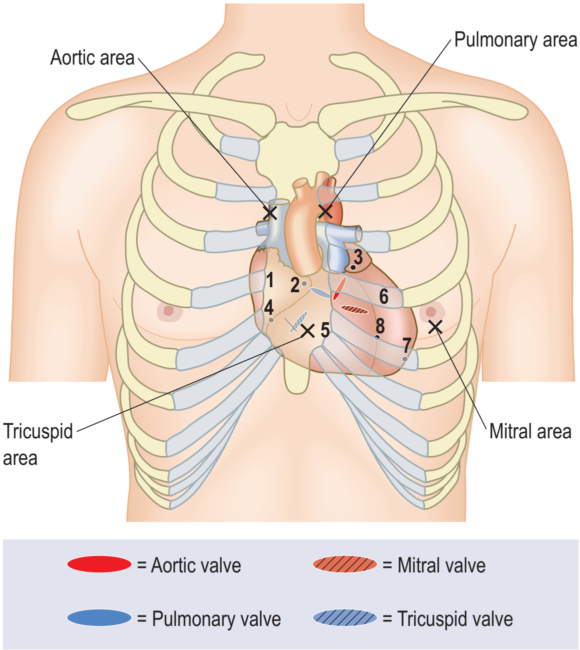


Figure 3.4 Auscultatory sites and surface markings of the heart valves: 1, right atrium; 2, right atrial appendage; 3, left atrial appendage; 4, atrioventricular groove; 5, right ventricle; 6, left ventricle; 7, apex of the heart; 8, anterior interventricular groove. Note: areas refer to where sound best heard, not anatomical location of the valve.

■ **Second heart sound (S2).** S2 ('*dub*') comprises aortic valve closure (A2) followed by pulmonary valve closure (P2) at the onset of diastole. Diastole is normally longer than systole. S2 is of slightly lower intensity than S1. Normally A2–P2 is slightly split (< 0.05 seconds apart) and A2 comes first – think of the efficient left ventricle contracting swiftly, offloading its stroke volume compared with the lower pressure within the right side of the heart.

There are four types of S2 splitting (Table 3.8).

The intensity of S2 may be altered by disease (Table 3.9).

■ **Third heart sound (S3).** This is described in Box 3.2.

■ **Fourth heart sound (S4).** This is described in Box 3.2.

Added sounds

- Listen for added sounds (Box 3.3).

Murmurs

Heart murmurs result from vibrations in the bloodstream and surrounding heart and great vessels as a result of turbulent flow.

- Try to determine the character, location and radiation of any murmur you hear (Box 3.4).
- Try to grade the intensity or loudness of any murmur you hear (Table 3.10).
- Try to determine the timing (with the carotid pulse) and duration of any murmur you hear (Table 3.11). Whilst this is expected by examiners and straightforward in theory, many candidates find timing difficult; what sounded like the typical whispering decrescendo murmur of aortic regurgitation suddenly becomes mitral regurgitation on the basis of dubious timing when all the evidence is with the former and against the latter. Keep in mind that the character of a murmur is more compellingly helpful than anything else when you might otherwise 'hedge your bets.'

Table 3.7 Abnormalities of S1 intensity

Loud S1	**Soft S1**	**Variable S1**
Tachycardia (shortened diastolic filling time, and faster valve closure)	Bradycardia (prolonged diastolic filling time)	Atrial fibrillation Ventricular ectopic beats
Short PR interval (atrial contraction precedes ventricular contraction in an unusually short time, again with faster valve closure)	Long PR interval (first-degree heart block)	Complete heart block
Mitral stenosis with pliable valve (high left atrial pressure forces leaflets further apart during atrial systole so that they are very far apart by the end of ventricular diastole and come together again more forcefully) Tricuspid stenosis	Mitral stenosis with non-pliable valve (anterior leaflet immobile owing to rigid calcification) Mitral regurgitation and left ventricular failure (imperfect closure or coaptation of leaflets)	
Increased atrioventricular flow in high cardiac output states	Poor chest wall conduction	

Table 3.8 Types of S2 splitting

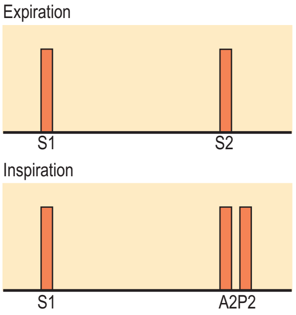
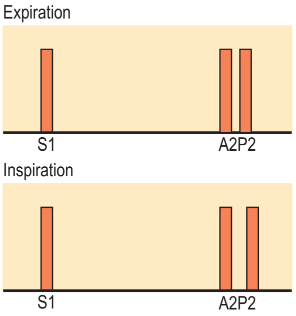
Type of splitting		Explanation	Causes (all splitting best heard at left sternal edge with diaphragm)
Inspiratory splitting		Reduced intrathoracic pressure on inspiration ‘sucks’ blood into the pulmonary vessels of the lungs. There is increased venous return and inflow to the right ventricle, which increases right ventricular stroke volume and right ventricular ejection time and so delays right ventricular emptying and thus P2. *In short, more blood is flowing through the right side of the heart in inspiration.* This is entirely logical because the lungs need more blood in inspiration for oxygenation purposes Blood is ‘held back’ from entering the left side of the heart by the reduced intrathoracic pressure and this decreased blood flow out of the lungs into the left side of the heart gives rise to earlier left ventricular emptying and an earlier A2 The diminished cardiac output during inspiration also explains why blood pressure falls and heart rate rises in inspiration The converse of these rules applies in expiration	The normal physiological situation
Accentuated physiological splitting and expiratory splitting		Physiological splitting is accentuated by right ventricular volume overload. Splitting that persists in expiration is usually pathological, and occurs when right ventricular emptying is further delayed or when left ventricular emptying is fast.	Splitting may be accentuated, normal or diminished in pulmonary hypertension depending upon the cause, pulmonary vascular resistance and the degree of right ventricular decompensation Delayed right ventricular emptying Right bundle branch block (delayed activation) Pulmonary embolism Pulmonary stenosis (prolonged right ventricular contraction) Right ventricular failure (right ventricular volume overload) Fast left ventricular emptying Mitral regurgitation (some ejection into left atrium) Ventricular septal defect (if shunted to right) Left ventricular ectopics and left ventricular pacing

Table 3.8 Types of S2 splitting—cont'd

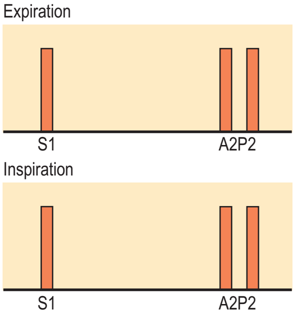
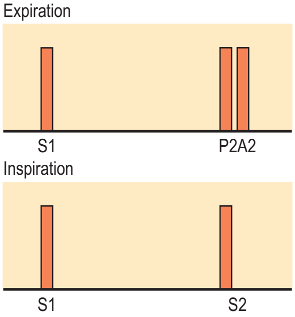
Type of splitting		Explanation	Causes (all splitting best heard at left sternal edge with diaphragm)
Wide and fixed splitting		Equalisation of volume loads between the two atria occurs in an atrial septal defect producing a common chamber. The proportion of blood contributed to the right atrium by the left atrium and the vena cava varies reciprocally throughout the respiratory cycle such that right ventricular inflow (and thus volume and duration of right ventricular ejection) is constant or *fixed* throughout the respiratory cycle. Since the right side of the heart is maximally overloaded, systole is prolonged and cannot be further delayed *(wide and fixed)*	Atrial septal defect
Reversed (paradoxic) splitting		Left ventricular emptying is delayed or right ventricular emptying is fast	Delayed left ventricular emptying Left bundle branch block Aortic stenosis Hypertrophic obstructive cardiomyopathy Systemic hypertension Left ventricular failure Fast right ventricular emptying Right ventricular pacing

Table 3.9 Abnormalities of S2 intensity

Loud S2	Soft S2
Tachycardia Systemic hypertension: loud A2 (forceful aortic valve closure due to high aortic pressures) Pulmonary hypertension: loud P2 (high pulmonary pressure) Congenital aortic stenosis (mobile but narrowed valve closes suddenly at end of diastole)	Severe aortic stenosis with calcified valve (reduced movement of leaflets) Aortic regurgitation (leaflets cannot coapt)

Table 3.10 Intensity of murmurs

Grade	Description
1	Very soft, heard only by experts
2	Heard by non-expert in optimum conditions
3	Easily heard but no thrill
4	Loud with thrill
5	Very loud with easily palpable thrill
6	Extremely loud and heard without stethoscope

Murmurs and physiological manoeuvres

- **Murmurs and respiration.** Right-sided heart murmurs are louder in inspiration because in inspiration blood flow increases through the right side of the heart. Left-sided heart murmurs are louder in expiration because in expiration blood flow increases through the left side of the heart.
- **Murmurs and dynamic auscultation.** Subtle murmurs may be enhanced by certain manoeuvres (Table 3.12). Tell the examiners that you would consider them but never ask a patient to perform these unless directed to do so by examiners.

Additional examination

Complete cardiovascular system examination includes assessment of lower limb pulses and examining for pulmonary, sacral and lower limb oedema.

Box 3.2 Extra heart sounds

Third heart sound (S3)

S3 is a low-pitched sound just after S2 (causing a gallop rhythm – 'Tennessee' or 'lub-dub-d' or 'd-d-d'). It is due to rapid ventricular filling in early diastole from a very full or engorged left atrium such that blood crashes into the left ventricle with a 'boing'. A left-sided S3 is best heard with the bell at the apex in the left lateral position in expiration. A right-sided S3 is best heard at the left sternal edge in inspiration. S3 occurs normally in healthy children, young adults, athletes, pregnancy, fever and other hyperdynamic states, but usually signifies a heart under strain as in heart failure or mitral regurgitation. Some physicians describe a 'tictac' rhythm in which S1 and S2 appear to be in a hurry ('lub-dub'-'lub-dub'-'lub-dub' becomes 'dd'-'dd'-'dd' ') just before a true gallop arises (the heart anticipating S3!) or coexisting with gallops.

Fourth heart sound (S4)

S4 is a low-pitched, presystolic sound occurring before S1 as a result of vigorous atrial contraction filling a stiff (less compliant) ventricle ('d-lub-dub'). As the mitral valve opens, the left atrium is 'looking down into a half full ventricle'. S4 peaks in intensity at the left ventricular apex and is heard best with the bell in the left lateral position. There may be palpable or even visible presystolic distension of the left ventricle. S4 may be accentuated by isotonic and isometric exercise. It may occur in systemic hypertension, aortic stenosis, left ventricular hypertrophy, ischaemic heart disease and restrictive cardiomyopathies. Most typically, it occurs in heart failure and simply represents a 'tired heart'; it is also common in acute myocardial infarction. It is always pathological. It cannot occur in atrial fibrillation.

S3 and S4 are often never detected by doctors but become easier to detect if you are expecting them, in heart failure for example. If S1and S2 appear in a hurry (tictac rhythm or 'dd'), then S3 or S4 may become apparent ('dd'-'d'-'dd'-'d'-'dd'-'d', where 'd' is S3 if detected just after 'dd' or S4 if detected just before 'dd'). If the heart rate is very fast, S3 and S4 may be superimposed as one audible sound. It does not necessarily imply a heart under stress unless one or both sounds persist when the heart is slowed. If both S3 and S4 are present the situation is a quadruple rhythm, a sign of severe ventricular dysfunction.

Summary

A summary of the cardiovascular examination sequence is in the Summary box.

SUMMARY BOX – CARDIOVASCULAR SYSTEM EXAMINATION SEQUENCE

- ◆ Look at the hands and arms for clubbing, peripheral cyanosis, xanthomata or peripheral signs of endocarditis.
- ◆ Look at the face for central cyanosis, pallor, a malar flush, corneal arcus or xanthelasmata.
- ◆ Determine the height of the jugular venous pulse and any abnormal waveform.
- ◆ Determine pulse rate, rhythm and character.
- ◆ Ask for the blood pressure.
- ◆ Determine the position of the apex and any abnormalities in apex beat character.
- ◆ Feel for a right ventricular heave.
- ◆ Feel for thrills.
- ◆ Ask yourself if pulse character, blood pressure and apex position predict any valve abnormality.
- ◆ Listen for S1 and S2; note any abnormal intensity of S1 and any abnormal splitting of S2.
- ◆ Listen for any S3 or S4.
- ◆ Listen for added sounds.
- ◆ Listen for murmurs.
- ◆ Consider the character, location, radiation, intensity and timing of murmurs (but give greatest attention to character).
- ◆ Remember to listen in the left lateral position and with the patient sitting forward.

Box 3.3 Added sounds

Opening snap (OS)

This is a brief, high-pitched, early diastolic sound occurring as the mitral valve is forced open by high left atrial pressure in mitral stenosis. The S2–OS interval is shorter the higher the left atrial pressure.

Ejection click or sound

This is a sharp, high-pitched sound in early systole soon after S1. It may occur in non-calcified aortic stenosis or pulmonary stenosis with a pliable valve, the mechanism similar to an opening snap and the sound preceding the typical ejection systolic murmur.

Mid-systolic (non-ejection) click

This may occur in mitral valve prolapse as one or both leaflets prolapse into the left atrium. There may be an accompanying late systolic murmur of mitral regurgitation.

Metallic prosthetic sounds

These may be audible without auscultation.

Pericardial knock

This is a third-heart-sound equivalent heard in diastole in constrictive pericarditis.

Pericardial friction rub

This is a scratching presystolic, systolic or early diastolic sound heard best with the diaphragm. It is due to pericarditis.

Box 3.4 Character, location and radiation of murmurs

Specific murmurs are described in more detail in individual cases. The location and radiation helps diagnostically. For example, aortic stenosis murmurs are usually loudest in the right second intercostal space and may radiate to the carotids; mitral regurgitation murmurs are often loudest at the apex and may radiate to the axilla (especially if the anterior leaflet is mostly affected) or the left sternal border and base of the heart (especially if the posterior leaflet is mostly affected). As a general rule, aortic murmurs tend to radiate more than mitral murmurs. However, the character or quality of a murmur is invariably more helpful than its location. You are the same person wherever you go – murmurs are no different.

Table 3.11 Timing of murmurs

Timing		Mechanism	Causes
Systolic murmurs	Pansystolic murmur	Flow between two chambers that have widely different pressure thoughout systole	Mitral regurgitation Tricuspid regurgitation Ventricular septal defect Sometimes aorto-pulmonary shunt
	Mid or ejection systolic murmur	Cresendo–decrescendo in shape (the sound of a 'woodcutter sawing wood in a forest') as pressure rises and falls	Aortic stenosis Pulmonary stenosis HCM Pulmonary flow murmur of ASD
	Early systolic murmur (unusual)		Large VSD with pulmonary hypertension Very small VSD Triscuspid regurgitation without pulmonary hypertension
	Late systolic murmur	Mitral regurgitation after the valve has clicked open in mitral valve prolapse	Mitral valve prolapse Mitral regurgitation from papillary muscle dysfunction
Diastolic murmurs	Early diastolic murmur	Begins with or shortly after S2 as soon as ventricular pressure falls below pressure in the aorta or pulmonary artery High-pitched, whispering and decrescendo	Aortic regurgitation Pulmonary regurgitation
	Mid-diastolic murmur	Disproportion between valve orifice and flow rate	Mitral stenosis Tricuspid stenosis Atrial myxoma *Carey Coombs* murmur of acute rheumatic fever attributed to mitral valve inflammation In severe aortic regurgitation, a mid-diastolic murmur (*Austin Flint murmur*) may arise at the anterior mitral valve leaflet as jets of blood from the aortic root and left atrium collide
	Presystolic murmur or presystolic accentuation of murmurs	Typical of mitral stenosis when the pressure-overloaded left atrium forcefully contracts and the mid-diastolic murmur crescendos into S1; occurs only in sinus rhythm	Mitral stenosis Tricuspid stenosis Atrial myxoma
Continuous murmurs	Combined systolic and diastolic murmurs may appear to fill cardiac cycle but are not continuous murmurs, by definition	Starts in systole, peaks near S2 and continues through all or much of diastole	Patent ductus arteriosus Arteriovenous fistulae (coronary, pulmonary, systemic) Aortic coarctation Venous hum Mammary soufflé (late pregnancy / early postpartum)

ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; VSD, ventricular septal defect.

Table 3.12 Effect of dynamic auscultation on murmurs

Manoeuvre	Effect on murmur		
	Most murmurs, e.g. mitral regurgitation, aortic stenosis	Mitral valve prolapse	Hypertrophic cardiomyopathy

Table 3.12 Effect of dynamic auscultation on murmurs—cont'd

Manoeuvre		**Effect on murmur**		
Valsalva strain phase		Softer and shorter because less blood is flowing in the heart	Louder and longer and follows earlier click because prolapse is enhanced when the heart is underfilled; this may be because a greater left ventricular end-diastolic volume exerts tension on the valve that maintains it in normal position; further, a left atrium filled with blood may counteract prolapse	Louder because reduced heart filling in diastole worsens the subsequent dynamic obstruction
During the strain phase (forceful expiratory pressure against a closed glottis) there is raised intrathoracic pressure leading to reduced right and left ventricular filling (reduced preload to both ventricles); this leads to reduced cardiac output and blood pressure falls and heart rate rises to compensate. *Note from* Table 3.8 *that reduced intrathoracic pressure in inspiration augments venous return, the opposite rule to the strain phase of Valsalva, but that both inspiration and the strain phase of Valsalva lead to a fall in blood pressure and cardiac output – in inspiration the negative pressure in the lungs 'sucks' blood from the right side of the heart and 'holds it back' from entering the left side of the heart (blood pools in the pulmonary vessels during inspiration for oxygenation purposes); in the strain phase of Valsalva, the positive intrathoracic pressure impedes venous return into the thorax, and reduced delivery of blood to the left side of the heart is the natural consequence. Thus in both inspiration and the strain phase of Valsalva cardiac output falls with a fall in blood pressure and rise in heart rate, although stretch receptor and baroreceptor autonomic responses contribute to these responses in inspiration and the strain phase of Valsalva respectively*				
Valsalva release phase				
During the release phase there is a transient overshoot correction of blood pressure, which rises, and heart rate falls				
Position	**Standing**	Softer and shorter	Louder and longer and follows earlier click	Louder
	Reduces venous return and murmurs follow the same rules as strain phase of Valsalva			
	Squatting or passive leg raising	Louder and longer	Softer and shorter and follows later click	Softer
	Enhance venous return and have the opposite effect on murmurs to strain phase of Valsalva and standing			
Exercise	**Isometric (e.g. sustained hand grip for 20–30 seconds)**	Aortic stenosis softer Most other murmurs louder	Softer and shorter and follows later click	Softer
	Increases systemic blood pressure (afterload) and heart rate and generally opposite effect on murmurs to strain phase of Valsalva and standing, although aortic stenosis murmurs may be softer because of a decreased gradient across the valve. Compare this with isotonic exercise (e.g. jogging), which also increases blood flow through the heart			

Cases

CASE 3.1 MITRAL STENOSIS

Instruction

This 65-year-old woman is thought to have a heart murmur. She is short of breath on exercise. Please examine her pulse, and palpate and auscultate her heart. Tell the examiners the signs you elicit, and discuss your proposed management.

Recognition

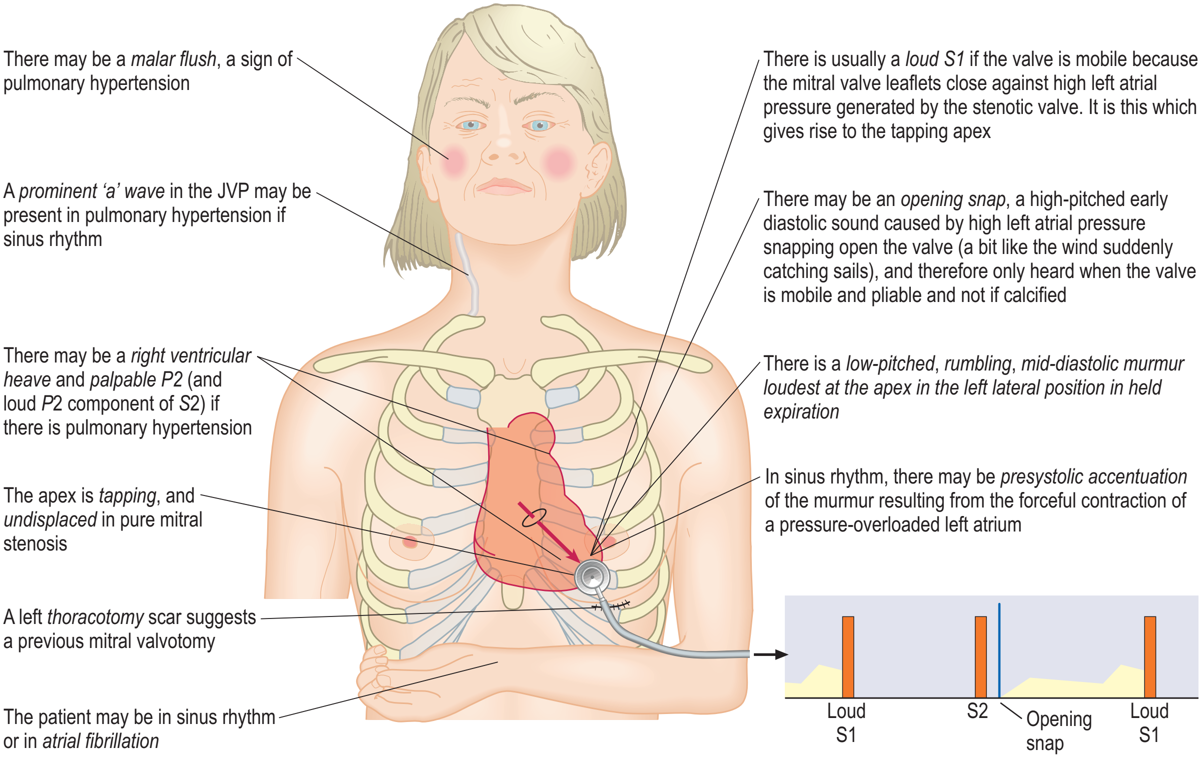
Signs of mitral stenosis are shown in Figure 3.5.

Interpretation

Confirm the diagnosis

Listen in the left lateral position and in expiration to accentuate the murmur. The differential diagnosis includes:

- Tricuspid stenosis (rare, louder in inspiration)
- Atrial myxoma (rare, fever, constitutional symptoms, raised inflammatory markers)
- Carey Coombs murmur (acute rheumatic fever)
- Austin Flint murmur (see Case 3.4).


There may be a *malar flush*, a sign of pulmonary hypertension

A *prominent 'a' wave* in the JVP may be present in pulmonary hypertension if sinus rhythm

There may be a *right ventricular heave* and *palpable P2* (and loud *P2* component of *S2*) if there is pulmonary hypertension

The apex is *tapping*, and *undisplaced* in pure mitral stenosis

A left *thoracotomy* scar suggests a previous mitral valvotomy

The patient may be in sinus rhythm or in *atrial fibrillation*

There is usually a *loud S1* if the valve is mobile because the mitral valve leaflets close against high left atrial pressure generated by the stenotic valve. It is this which gives rise to the tapping apex

There may be an *opening snap*, a high-pitched early diastolic sound caused by high left atrial pressure snapping open the valve (a bit like the wind suddenly catching sails), and therefore only heard when the valve is mobile and pliable and not if calcified

There is a *low-pitched*, *rumbling*, *mid-diastolic murmur loudest at the apex in the left lateral position in held expiration*

In sinus rhythm, there may be *presystolic accentuation* of the murmur resulting from the forceful contraction of a pressure-overloaded left atrium

Figure 3.5 Mitral stenosis. JVP, jugular venous pulse.

Encountering a 'full-house' of signs is improbable and even when present they are difficult to elicit. Many physicians say they have never heard an opening snap. Atrial fibrillation renders a murmur difficult to time. But the rumbling murmur is characteristic, not unlike heavy rain on a tin roof, the rumble of a subway train or a buffalo stampede!

What to do next – consider causes

Tell the examiners that causes of mitral stenosis include:

- Rheumatic heart disease (the most common cause worldwide, but dramatically decreased over last 50 years in developed countries; in Australia, for example, where streptococcal infection is highly prevalent within the Aboriginal population, rheumatic heart disease is a major health burden)
- Congenital
- Left atrial myxoma
- Connective tissue disease.

Two-thirds of patients are female.

Consider severity / decompensation / complications

Signs of severe mitral stenosis are listed in Box 3.5.

Tell the examiners that:

Box 3.5 **Signs of severe mitral stenosis**

- Signs of pulmonary hypertension (Case 1.18)
- Short interval between S2 and opening snap (the shorter the interval the higher the left atrial pressure)
- Long diastolic murmur

- Pulmonary hypertension may be irreversible.
- Thromboembolic disease, especially stroke, may result from systemic emboli originating in the left atrium
- Infective endocarditis may lead to valve decompensation.
- Ortner's phenomenon is rare and refers to hoarseness resulting from an enlarged left atrium exerting pressure on the left recurrent laryngeal nerve supplying the vocal cord.
- Any situation that increases heart rate, such as exercise, pregnancy or sepsis, further increases the trans-mitral pressure gradient and can provoke increased pulmonary pressure and pulmonary oedema.

Consider function

Tell the examiners you would establish the limitations provoked by exertional dyspnoea and consider fitness for surgery.

Discussion

What happens to the valve pathologically?

The mitral valve is funnel shaped, dipping into the left ventricle. In mitral stenosis the valve leaflets and chordae tendinae are diffusely thickened by fibrosis and calcification resulting in their fusion, thickening and reduced mobility. These narrow the apex of the funnel. The orifice reduces from its normal 4 cm^2 to 1 cm^2 or less, and blood can only be propelled into the ventricle by an abnormally elevated left atrial pressure.

What is the most common presenting symptom of mitral stenosis?

Exertional dyspnoea.

Why should patients experience exertional dyspnoea?

As blood flow increases with exercise across the mitral valve, the increased left atrial pressure needed to propel blood across the valve raises pulmonary venous and capillary pressures, which reduce pulmonary compliance, and pulmonary artery pressure increases.

Tachycardia also diminishes diastole disproportionately more than systole and thus the time for flow across the stenosed valve is reduced. Therefore at any given level of cardiac output, tachycardia increases the transvalvular gradient and further elevates left atrial pressure.

When the valve orifice is reduced to 1 cm^2, a left atrial pressure of 25 mmHg is needed to maintain normal cardiac output. Pulmonary oedema may occur if there is a sudden surge of flow across a tight valve.

Eventually there is decreased cardiac output on exertion and at rest. The ability of the left atrium to generate sufficient pressure to maintain transvalvular flow is overcome.

What other symptoms may occur in mitral stenosis?

Symptoms may be the result of atrial arrhythmias, including premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter and atrial fibrillation. Haemoptysis, due to the rupture of pulmonary–bronchial venous connections in pulmonary venous hypertension, is unusual but occurs in patients with raised left atrial pressure but without significantly increased pulmonary vascular resistance.

How does pulmonary hypertension arise?

Passive transmission backwards of raised left atrial pressure leads to raised pulmonary venous and capillary pressure, pulmonary arteriolar constriction triggered by pulmonary venous hypertension (reactive pulmonary hypertension), interstitial oedema and pressure damage to and fibrosis or obliteration of the pulmonary vascular bed.

What are the diagnostic criteria for rheumatic fever?

Rheumatic fever (Box 3.6) and rheumatic heart disease remain common in the developing world, the latter a common usher for infective endocarditis. In the developed world the legacy of rheumatic fever remains, most commonly as mitral stenosis and sometimes as other valvular heart disease (VHD), but VHD in developed countries is now most commonly degenerative. Two major criteria or one major and two minor criteria plus evidence of antecedent group A streptococcal infection are required for a diagnosis of rheumatic fever.

List some features the electrocardiogram (ECG) might show in mitral stenosis

- p pulmonale if pulmonary hypertension (tall and peaked in II and upright in V1 if severe)
- Atrial fibrillation
- Right axis deviation
- Right ventricular hypertrophy in pulmonary hypertension

List some features the chest X-ray might show in mitral stenosis

- Enlarged left atrium
- Widened carinal angle
- Kerley B lines (indicating a left atrial pressure > 20 mmHg)
- Alveolar oedema
- Pulmonary haemosiderosis (haemosiderin containing macrophages in airways)

What might echocardiography be used to assess in mitral stenosis?

- Transvalvular gradient
- Mitral valve area: 1.5–2.2 cm^2 mild stenosis, 1.0–1.5 cm^2 moderate stenosis, < 1 cm^2 severe stenosis

Box 3.6 **Diagnostic criteria (Jones) for rheumatic fever**

Major criteria

- Carditis
- Migratory polyarthritis
- Erythema marginatum
- Chorea
- Subcutaneous nodules

Minor criteria

- Fever
- Arthralgia
- Raised acute-phase reactants
- Prolonged PR interval

- Rigidity and nature of valve disease
- Cardiac chamber dimensions
- Pulmonary artery pressure
- The presence of any associated mitral regurgitation

What is the place of cardiac catheterisation?

This may provide more accurate assessment of pulmonary artery and heart chamber pressures, and can be used to assess both pressure gradient and flow rate across the valve. Left ventricular end-diastolic pressure (LVEDP) is normal in pure mitral stenosis. It is often raised, however, with coexisting impaired left ventricular function because of ischaemic heart disease, mitral regurgitation, aortic valve disease or systemic hypertension. The end-diastolic gradient between left atrial pressure and LVEDP is a guide to severity and need for surgery, and surgery would not normally be performed for a gradient of < 5 mmHg. Theoretically a gradient is a rate of change and the term pressure drop is sometimes used, although most argue that gradient is an appropriate term because the pressure changes continuously as blood crosses a valve.

How might you clinically detect if there is significant concomitant mitral regurgitation?

There would be significant diminution of S1 and the opening snap, together with a pansystolic murmur.

Which treatments may be considered for mitral stenosis?

All patients should be considered for anticoagulation if there are no contraindications, and receive antibiotic prophylaxis during procedures. Most asymptomatic patients with mild to moderate mitral stenosis can be reviewed annually with echocardiography. Patients with symptoms and a valve area < 1.5 cm^2 should be considered for intervention by means of percutaneous balloon mitral valvuloplasty (BMV) or surgical valve replacement. Pulmonary artery hypertension and recurrent emboli despite adequate anticoagulation may also be indications for surgery. BMV is preferred to valve replacement if the valve is mobile and relatively undistorted, provided there is no / minimal mitral regurgitation and no left atrial thrombus, and can delay valve replacement by many years in suitable patients. There is controversy as to whether patients with severe mitral stenosis (valve area < 1.0 cm^2) and severe pulmonary hypertension (> 60 mmHg) should undergo BMV or valve replacement to prevent right ventricular failure. Transcatheter mitral valve repair and minimally invasive valve replacement are emerging strategies.

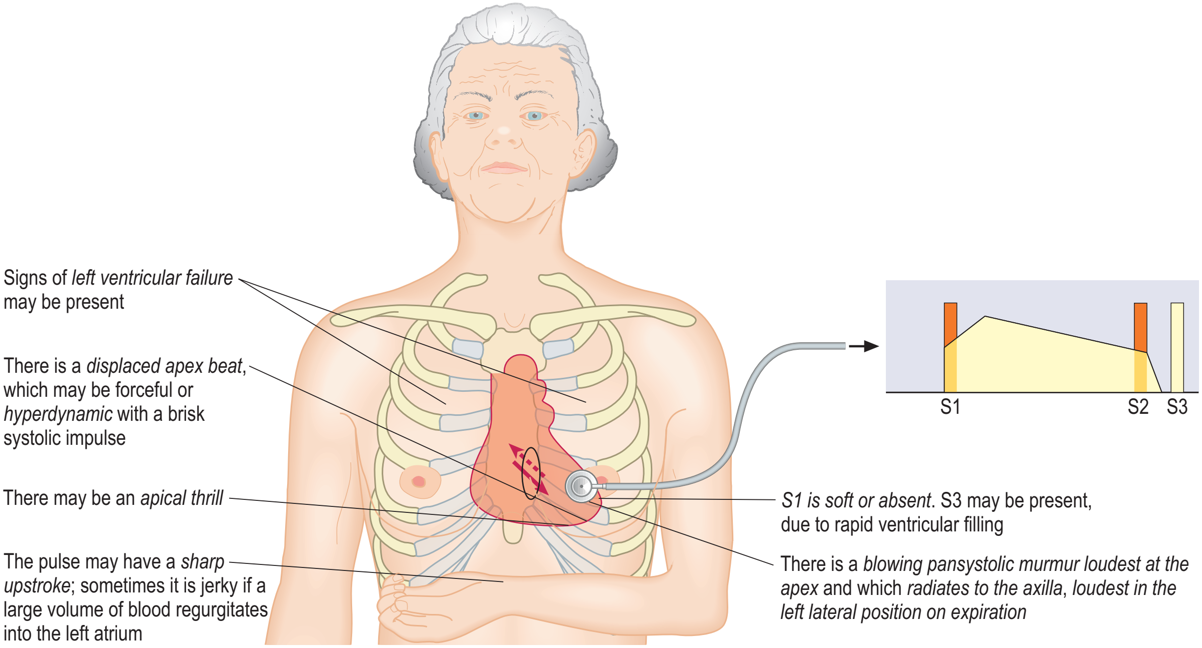
CASE 3.2 MITRAL REGURGITATION

Instruction

This 66-year-old woman is thought to have a heart murmur. Please palpate and auscultate her praecordium and discuss your findings.

Recognition

Signs of mitral regurgitation are shown in Figure 3.6.



Signs of *left ventricular failure* may be present

There is a *displaced apex beat*, which may be forceful or *hyperdynamic* with a brisk systolic impulse

There may be an *apical thrill*

The pulse may have a *sharp upstroke*; sometimes it is jerky if a large volume of blood regurgitates into the left atrium

S1 is soft or absent. S3 may be present, due to rapid ventricular filling

There is a *blowing pansystolic murmur loudest at the apex* and which *radiates to the axilla*, *loudest in the left lateral position on expiration*

Figure 3.6 Mitral regurgitation.

Interpretation

Confirm the diagnosis

Listen in the left lateral position and in expiration to accentuate the murmur. The differential diagnosis includes:

- Tricuspid regurgitation (pansystolic murmur louder in inspiration, 'V' waves, pulsatile liver)
- Ventricular septal defect
- Other systolic murmurs, e.g. ejection systolic murmur of aortic stenosis radiating to carotids

What to do next – consider causes

Mitral regurgitation is the most common valvular heart disease (VHD) and can result from malfunction of the valve leaflets, the valve annulus, the chords, the papillary muscles or the underlying myocardium. Tell the examiners that causes include the following.

Primary (valve problem)

- Degenerative mitral valve disease (also known confusingly as mitral valve prolapsed or myxomatous mitral valve disease) is the most common cause; the term degenerative encompasses a spectrum of pathologies leading to varying degrees of leaflet redundancy, thickening or thinning, and lengthening or rupture of the chordate, in essence all leading to systolic prolapse of one or both leaflets back into the left atrium
- Infective endocarditis is the second most common cause (tends to be acute)
- Rheumatic mitral regurgitation is rare

Secondary (left ventricular problem)

- Ischaemic heart disease / myocardial infarction with left ventricular dysfunction or papillary muscle rupture
- Cardiomyopathy

Consider severity / decompensation / complications

Signs of severe mitral regurgitation are listed in Box 3.7.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (fatigue, exertional dyspnoea, orthopnoea) and consider fitness for surgery (mitral regurgitation is seldom treated surgically).

Box 3.7 **Signs of severe mitral regurgitation**

- Left ventricular failure is the most obvious feature of advanced mitral regurgitation
- When the left atrium is markedly enlarged, it may be palpable at the left sternal edge and resemble a right ventricular heave
- Combined retraction of the left ventricle and expansion of the left atrium during systole may create a characteristic chest wall rocking motion (rare)
- Progressively rising pulmonary venous and capillary pressure may progress to raised pulmonary artery pressure with signs of right-sided heart failure.

Discussion

What is the pathophysiology of mitral regurgitation and does it tend to progress?

During systole there is ejection of blood into both aorta and left atrium. This reduces left ventricular afterload and left ventricular tension or pressure but ultimately creates a volume-overloaded left side of the heart as the left ventricle becomes the recipient of its intended volume of blood plus that which it ejected aberrantly into the left atrium. Both left atrium and left ventricle enlarge. Irrespective of cause, mitral regurgitation tends to progress, because the enlarging left atrium pulls the posterior mitral valve leaflet away from the orifice and the dilating left ventricle enhances the regurgitation. Eventually, the enlarging left ventricle can no longer accommodate and compensate for this state of affairs, often after many years, and breathlessness develops.

List some features the electrocardiogram (ECG) might show in mitral regurgitation

- Left atrial enlargement (P mitrale)
- Atrial fibrillation if left atrium enlarged
- Left ventricular hypertrophy (often coexists with dilatation)

List some features the chest X-ray might show in mitral regurgitation

- Left atrial and left ventricular enlargement
- Signs of left ventricular failure

What other investigations are available in VHD?

Echocardiography has traditionally been two-dimensional but three-dimensional echocardiography is emerging, with most experience in mitral VHD.

Cardiac magnetic resonance imaging provides accurate assessment of valve function of any valve, particularly quantification of regurgitation, and accurate left ventricular mass and volume.

Cardiac computed tomography may be used to exclude coronary disease prior to valve surgery in selected patients with VHD.

What treatments may be considered for mitral regurgitation?

Management depends upon cause. Asymptomatic patients should receive antibiotic prophylaxis during procedures and be followed up with serial echocardiography. Asymptomatic patients with moderate or worse mitral regurgitation should be followed at least annually with echocardiography. Patients with severe degenerative mitral regurgitation should be offered valve repair before the onset of limiting symptoms or left ventricular dysfunction. Surgery for ischaemic mitral regurgitation is less successful, but should be considered in patients with moderate or severe mitral regurgitation undergoing coronary artery bypass grafting and in patients with severe mitral regurgitation and breathlessness. Percutaneous approaches are an emerging alternative in some patients.

CASE 3.3 AORTIC STENOSIS

Instruction

Please examine this 80-year-old woman's cardiovascular system and discuss your findings.

Recognition

Signs of aortic stenosis are shown in Figure 3.7.

Interpretation

Confirm the diagnosis

Listen with the patient sitting forward and in expiration to accentuate the murmur. The differential diagnosis includes:

- Pulmonary stenosis (murmur louder on inspiration, radiates to left clavicle) but this is very rare
- Hypertrophic (obstructive) cardiomyopathy
- Other systolic murmurs, e.g. pansystolic murmur of mitral regurgitation, loudest at apex.

What to do next – consider causes

Tell the examiners that causes include:

- Calcification-induced degeneration of normal tri-leaflet valve (by far the commonest cause)
- Congenital bi-leaflet valve (affects 1–2% of people, and tends to present in the fifth and sixth decades with accelerated calcification-induced degeneration)
- Rheumatic heart disease, usually with associated mitral valve disease (now much less common).

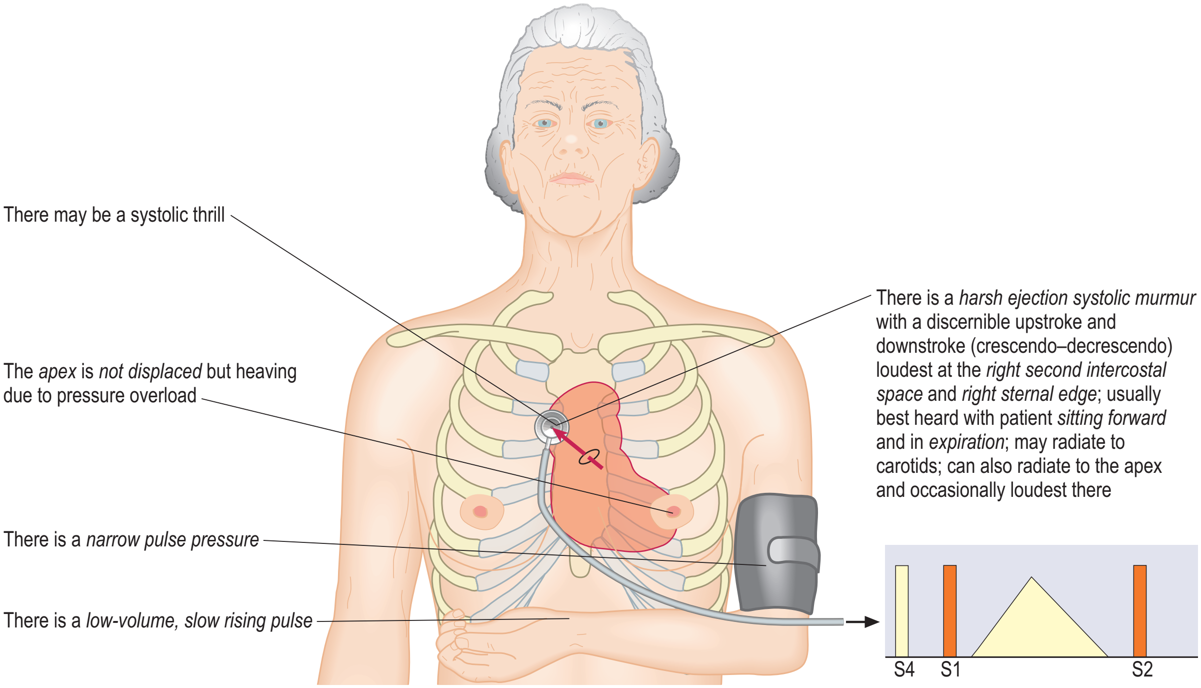
Consider severity / decompensation / complications

Signs of severe aortic stenosis are listed in Box 3.8. Additionally, an early peaking murmur may be associated with a less stenotic valve and a late peaking murmur more severe stenosis.

Average time to death with angina or syncope is 3 years, with dyspnoea 2 years and with heart failure 1.5 years. Asymptomatic patients even with severe stenosis have an excellent prognosis with surgery.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (gradually decreasing exercise tolerance is usually the presenting symptom) and consider fitness for surgery.



There may be a systolic thrill

The *apex* is *not displaced* but heaving due to pressure overload

There is a *narrow pulse pressure*

There is a *low-volume, slow rising pulse*

There is a *harsh ejection systolic murmur* with a discernible upstroke and downstroke (crescendo–decrescendo) loudest at the *right second intercostal space* and *right sternal edge*; usually best heard with patient *sitting forward* and in *expiration*; may radiate to carotids; can also radiate to the apex and occasionally loudest there

Figure 3.7 Aortic stenosis.

Box 3.8 **Signs of severe aortic stenosis**

- Small-volume pulse
- Narrow pulse pressure
- Soft S2 (the valve leaflets neither open nor close well rather than crisply opening and snapping shut)
- Reversed S2
- Thrill / heave
- Left ventricular failure with S4

Box 3.9 **Pathophysiology of aortic stenosis**

- Aortic stenosis is a condition of pressure overload in which reduced systolic excursion through thickened valve cusps results in a left ventricular systolic pressure rise and left ventricular hypertrophy. The left ventricle is essentially 'weight lifting' or straining against progressive weights – increasingly so as the valve progressively narrows – as it does with systemic hypertension. The ejection pressure rises and falls between peaks in mid-systole to produce the ejection systolic murmur.
- The stroke volume ejected from the left ventricle is limited, and results in a small volume pulse that is slow rising.
- Because the obstructed valve limits the amount of pressure the systemically ejected jet can achieve, the pulse pressure is narrow with a low systolic component.

Discussion

How does the pathophysiology of aortic stenosis correlate with the pulse, pulse pressure and murmur?

This is described in Box 3.9.

Aortic stenosis is the commonest form of valvular heart disease, predominantly affecting older people.

Why might patients with aortic stenosis develop angina?

This might be due to:

- Outflow obstruction impairing coronary sinus filling
- Squeezing of coronary arteries by hypertrophied muscle
- Increased myocardial demand from hypertrophied muscle.

However, aortic stenosis is usually asymptomatic and the majority of patients with aortic stenosis and angina will have typical coronary artery disease.

Is there a difference between aortic sclerosis and aortic stenosis?

Aortic sclerosis refers to thickening of the valve because of calcification without stenosis and can progress over years to aortic stenosis. Once thought to be different conditions, they are now viewed as part of the same spectrum. Aortic stenosis is the commonest adult valve lesion and aortic sclerosis affects 20–30% of people over 65 years and 48% of those over 85 years. The pulse volume tends to be normal and the murmur does not radiate to the carotids. Aortic sclerosis is not usually of haemodynamic significance, but can be.

How does calcific aortic stenosis arise?

Traditionally it is attributed to degeneration of an ageing valve. However, many people over 80 years have no calcification, and increasingly calcific aortic stenosis is viewed as a chronic inflammatory condition, not dissimilar pathophysiologically to those mechanisms described for atherosclerosis in coronary artery disease. There is, not surprisingly, emerging evidence for the role for statin therapy in modifying this process. While non-specific thickening of the valve tips is very common in anyone over 80 years of age, calcific thickening characteristically results in irregular nodules on the aortic surfaces of the leaflets. Furthermore, the risk factors for calcific aortic stenosis are similar to those for coronary artery disease – age, male sex, smoking, dyslipidaemia, hypertension, diabetes, coronary heart disease, chronic kidney disease, hypercalcaemia.

Do you know of any unusual anaemia associations with aortic stenosis?

These include angiodysplasia (mechanism uncertain and association remains controversial) and microangiopathic haemolytic anaemia (mechanical chomping of blood cells).

List some other forms of left ventricular outflow obstruction

- Hypertrophic (obstructive) cardiomyopathy
- Discrete congenital subvalvular aortic stenosis
- Supravalvular aortic stenosis (uncommon, congenital)

List some features the electrocardiogram (ECG) might show in aortic stenosis

- Left ventricular hypertrophy
- ST segment depression and T-wave inversion (left ventricular strain) in leads I and aVL and in anterolateral precordial leads

What might the chest X-ray show in aortic stenosis?

This is normal unless a calcified valve is visible.

How is aortic stenosis severity determined by echocardiography?

The current gold standard for assessing severity is two-dimensional and Doppler echocardiography, although magnetic resonance imaging is increasingly helpful. Narrowing of the valve results in acceleration of blood flow

Table 3.13 Echocardiographic measurement of severity of aortic stenosis

	Normal	Mild	Moderate	Severe
Aortic valve area (cm^2)	3.0–4.0	> 1.5	1.0–1.5	< 1.0
Aortic jet velocity (m/s)	0.9–2.5	< 3	3–4	> 4
Mean gradient (mmHg)	< 25	< 25	25–40	> 40

across the valve and larger pre–post valve peak and mean pressure differences or gradients (Table 3.13). The peak pressure gradient across the aortic valve has a simple relationship with the aortic jet velocity and is described as four times the square of that velocity (modified Bernoulli equation). A peak velocity of 4 m/s, for example, gives a peak pressure gradient of $4 \times 4^2 = 64$ mmHg with a mean gradient of 40 mmHg. Patients may be asymptomatic despite severe stenosis.

What is the rate of progression of aortic stenosis?

In people with aortic sclerosis, progression to stenosis (arbitrarily defined as a peak post-valve velocity > 2.5 m/s or peak gradient > 25 mmHg) is relatively slow, with mean increases per year in peak post-valve velocity and peak gradient of 0.07 m/s and 1.4 mmHg, respectively. However, once stenotic, severity rates accelerate with average yearly increases of 0.3 m/s and 7–8 mmHg, corresponding to a decrease in valve area of 0.1 cm^2 per year.

Which drugs should be used with caution or avoided?

Excessive diuretic use should be avoided in severe aortic stenosis because diastolic dysfunction is common and an adequate preload is needed to maintain cardiac output. Although the evidence for so doing is limited, drugs that reduce afterload or preload, notably angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and nitrates, should be avoided with advancing severity (although increasing evidence supports a beneficial role for angiotensin inhibition). A reduction in afterload will increase the gradient across the valve. The heart responds by increasing cardiac output but cannot do so if preload is compromised. In practice, any antihypertensives should be used with caution but further evidence is needed to establish the dangers or possible benefits. In angina, beta blockers and even nitrates may be used with caution.

What treatments may be considered for aortic stenosis?

Despite advances in understanding of the pathophysiology of calcific aortic valve disease as an active disease process, no therapy clearly slows or reverses disease progression, although statins have exhibited benefit in some trials. Current management involves monitoring progression, ensuring antibiotic prophylaxis during procedures and, for those with severe symptoms, conventional medical therapy or aortic valve surgery. Surgery is indicated as soon as symptoms start, and may be considered if the left ventricular ejection fraction falls below 50%. Although often intuitively worrying to see patients with severe asymptomatic stenosis not proceed to surgery, annual mortality figures in this latter group are now less than 1% per year, pitched against a combined risk of aortic valve replacement (AVR) mortality (2–10% per year) and prosthesis-related complications (2–3% per year). Congenital bicuspid aortic valves account for half of all AVRs and are associated with aortic dilatation. As well as traditional AVR, percutaneous valve therapy is growing. Transcatheter aortic valve implantation is an established alternative in high-risk or inoperable patients. Balloon aortic valvuloplasty is enjoying new popularity. Patients requiring bypass grafting with aortic stenosis should undergo traditional AVR.

CASE 3.4 AORTIC REGURGITATION

Instruction

Please examine this 70-year-old man's cardiovascular system and discuss your findings.

Recognition

Signs of aortic regurgitation are shown in Figure 3.8.

Some eponymous signs of the hyperdynamic circulation in aortic regurgitation are given in Box 3.10.

Interpretation

Confirm the diagnosis

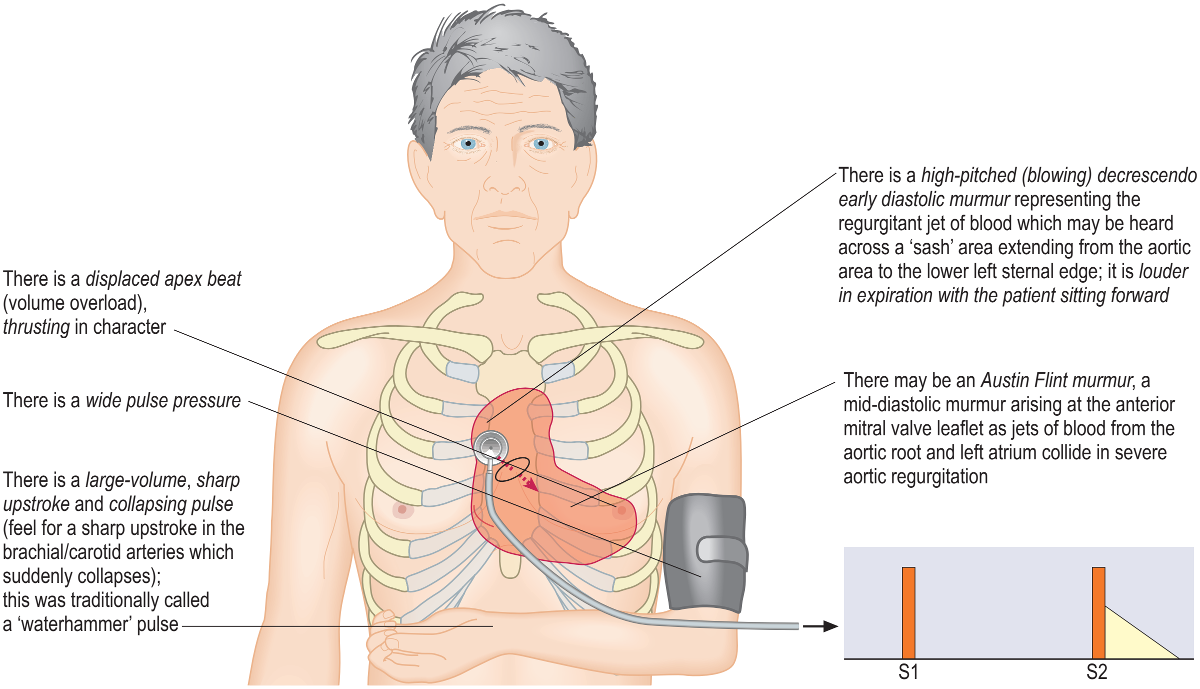
Listen with the patient sitting forward and in expiration to accentuate the murmur. The differential diagnosis includes:

- Pulmonary regurgitation, which is a similar murmur but loudest at the pulmonary area and louder in inspiration.

What to do next – consider causes

Tell the examiners that causes include:

- Infective endocarditis
- Prosthetic valve paravalvular leak – acute or chronic


There is a *displaced apex beat* (volume overload), *thrusting* in character

There is a *wide pulse pressure*

There is a *large-volume*, *sharp upstroke* and *collapsing pulse* (feel for a sharp upstroke in the brachial/carotid arteries which suddenly collapses); this was traditionally called a 'waterhammer' pulse

There is a *high-pitched (blowing) decrescendo early diastolic murmur* representing the regurgitant jet of blood which may be heard across a 'sash' area extending from the aortic area to the lower left sternal edge; it is *louder in expiration with the patient sitting forward*

There may be an *Austin Flint murmur*, a mid-diastolic murmur arising at the anterior mitral valve leaflet as jets of blood from the aortic root and left atrium collide in severe aortic regurgitation

Figure 3.8 Aortic regurgitation.

Box 3.10 **Eponymous signs in aortic regurgitation (some are hard to believe!)**

- Corrigan's sign – visible rise and fall of pulsation; often vigorous or 'dancing' brachial or carotid arteries
- De Musset's sign – head nodding with each pulsation (Abraham Lincoln probably had this)
- Quincke's sign – alternate flushing and paling of the skin at the nail bed while pressure is applied to tip of nail (may occur at mucous membranes)
- Lighthouse sign – flushing and paling of the forehead
- Traube's sign – pistol shot systolic and diastolic sounds heard at the femoral arteries
- Duroziez's sign – a systolic sound heard at the femoral artery when compressed proximally and a diastolic sound if compressed distally; essentially a to-and-fro sound at the femoral artery
- Muller's sign – uvula pulsation
- Rosenbach's sign – hepatic pulsation
- Gerhardt's sign – splenic pulsation (if enlarged)
- Landolfi's sign – change in pupil size synchronous with cardiac cycle

Box 3.11 **Signs of severe aortic regurgitation**

- Wide pulse pressure
- Soft S2
- Short early diastolic murmur (earlier equalisation of aortic and ventricular pressures)
- S3 / left ventricular failure
- Austin–Flint murmur
- Hill's sign (popliteal cuff exceeding brachial cuff systolic pressure by ≥ 20 mmHg; 20–39 mild, 40–59 moderate, ≥ 60 severe)

- Rheumatic heart disease
- Ankylosing spondylitis (kyphosis, question mark posture)
- Marfan's syndrome (tall, long extremities with arm span > height, arachnodactyly, high arched palate)
- Rheumatoid arthritis (rheumatoid hands)
- Syphilitic aortitis (rare).

Aortic regurgitation is more common in males, and usually due simply to an ageing degenerative valve. Of patients undergoing aortic valve surgery, about 50% have a problem with the valve itself (of which around 60% are bi-leaflet valves and 20% infective endocarditis) and 50% the aortic root.

Consider severity / decompensation / complications

Signs of severe aortic regurgitation are listed in Box 3.11.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic until too late) and consider fitness for surgery.

Box 3.12 **Pathophysiology of aortic regurgitation**

- The left ventricle dilates (and to an extent its wall thickens) to accommodate the increased blood volume that results from a reverse pressure gradient and regurgitation from aorta to left ventricle resulting from inadequate coaptation of the aortic valve cusps in diastole. This pressure gradient falls during diastole to produce the decrescendo of the early diastolic murmur.
- The total stroke volume ejected from the left ventricle (effective forward stroke volume plus regurgitated volume) is increased, resulting in a large-volume pulse with a sharp upstroke. This collapses when arterial pressure falls rapidly in late systole and diastole.
- Because there is high systolic outflow but aortic run-off back into the ventricle in diastole, the pulse pressure is wide, with increased systolic and decreased diastolic components; ultimately, of course, the stretching, floppy sack that is the left ventricle decompensates (heart failure) with decreased output.

Discussion

How does the pathophysiology of aortic regurgitation correlate with the pulse, pulse pressure and murmur?

This is described in Box 3.12.

What might the electrocardiogram (ECG) show in aortic regurgitation?

Left ventricular strain is common.

List some features the chest X-ray might show in aortic regurgitation

- Left ventricular enlargement
- Prominent aorta

What treatments may be considered for aortic regurgitation?

Surgery is the definitive treatment to halt volume overload. The aim is to replace the valve before significant left ventricular dysfunction occurs, the criteria for considering surgery being symptoms, left ventricular ejection fraction $< 50\%$, left ventricular end-systolic dimension > 50 mm or left ventricular end-diastolic dimension > 70 mm.

CASE 3.5 TRICUSPID REGURGITATION AND EBSTEIN'S ANOMALY

Instruction

Please examine this 48-year-old woman's cardiovascular system and discuss your findings.

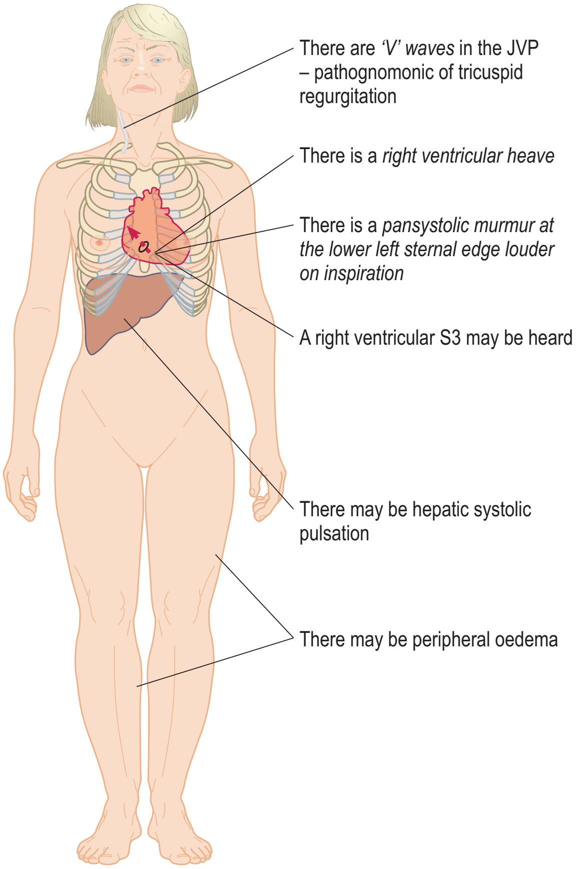

There are *'V' waves* in the JVP – pathognomonic of tricuspid regurgitation
There is a *right ventricular heave*
There is a *pansystolic murmur at the lower left sternal edge louder on inspiration*
A right ventricular S3 may be heard
There may be hepatic systolic pulsation
There may be peripheral oedema

Figure 3.9 Tricuspid regurgitation. JVP, jugular venous pulse.

Recognition

Signs of tricuspid regurgitation are shown in Figure 3.9.

Interpretation

Confirm the diagnosis

Listen in inspiration to accentuate the murmur. The differential diagnosis includes:

- Mitral regurgitation (murmur at apex radiating to axilla, louder in expiration)
- Other systolic murmurs, e.g. ejection systolic murmur of aortic stenosis.

What to do next – consider causes

Tell the examiners that tricuspid regurgitation is usually functional, secondary to dilatation of the annulus. It may occur in:

- Heart failure
- Right ventricular infarction

- Pulmonary hypertension of any cause (cor pulmonale, mitral stenosis, primary pulmonary hypertension)
- Eisenmenger's syndrome.

Primary causes include:

- Rheumatic heart disease
- Right-sided endocarditis
- Carcinoid syndrome.

Consider severity / decompensation / complications

Signs of severe tricuspid regurgitation are:

- Hepatic pulsation
- Peripheral oedema.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic until too late) and consider fitness for surgery.

Discussion

What other right-sided valve abnormalities do you know of?

- Tricuspid stenosis (rare; generally part of rheumatic heart disease)
- Pulmonary regurgitation (usually the result of dilatation of the pulmonary valve ring in pulmonary hypertension – Graham Steell murmur)
- Pulmonary stenosis (rare; may be congenital or due to carcinoid syndrome)

What are the indications for surgery in tricuspid regurgitation?

These include:

- Symptoms
- As concomitant procedure if severe tricuspid regurgitation and surgery for mitral valve disease
- As concomitant procedure for less severe tricuspid regurgitation and surgery for mitral valve disease, but pulmonary hypertension or tricuspid annular dilatation.

What do you know about Ebstein's anomaly?

This is congenital, isolated tricuspid regurgitation (without signs of pulmonary hypertension), which leads to cardiomegaly and right-sided heart failure. Ebstein's anomaly is characterised by downward displacement of the tricuspid valve into the right ventricle owing to anomalous attachment of the tricuspid leaflets. The abnormally situated tricuspid orifice produces an 'atrialised' portion of right ventricle, which lies between the atrioventricular ring and origin of the valve. The right ventricle is often hypoplastic. Cyanosis results because of right-to-left shunting at the atrial level (through a patent foramen ovale or an atrial septal defect).

CASE 3.6 OTHER RIGHT-SIDED HEART MURMURS

Instruction

Please examine this 28-year-old woman's cardiovascular system and discuss your findings.

Recognition

Signs of pulmonary regurgitation are shown in Figure 3.10.

Interpretation

Confirm the diagnosis

Listen in inspiration to accentuate the murmur. The differential diagnosis of right-sided heart murmurs includes:

- Tricuspid regurgitation
- Tricuspid stenosis (rare; generally part of rheumatic heart disease)
- Pulmonary stenosis (rare; may be congenital, e.g. Noonan's syndrome, or due to carcinoid syndrome).

What to do next – consider causes

Pulmonary regurgitation is usually due to dilatation of the pulmonary valve ring in pulmonary hypertension causing the classic Graham Steell murmur. Tell the examiners that other important causes include:

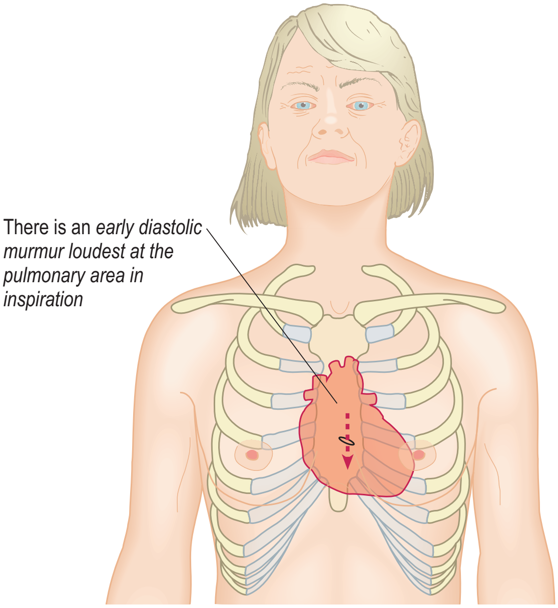

There is an *early diastolic murmur loudest at the pulmonary area in inspiration*

Figure 3.10 Pulmonary regurgitation.

- Infective endocarditis from intravenous drug use
- Carcinoid syndrome.

Consider severity / decompensation / complications

Valve decompensation is common in infective endocarditis.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic until too late) and consider fitness for surgery.

Discussion

Which valve is most commonly affected in infective endocarditis secondary to intravenous drug use?

Tricuspid valve endocarditis is common.

CASE 3.7 MIXED VALVE DISEASE

Instruction

This patient has a mixture of heart valve abnormalities. Please decide which valve abnormality is dominant.

Recognition

Aortic stenosis and mitral regurgitation is the commonest combination of valve abnormalities. Mixed mitral and mixed aortic valve disease is also common.

Mixed mitral valve disease

Pulse character, apex, S1 examination and the character of the murmur may help determine which is dominant (Table 3.14). Further, the presence of an S3 would imply the absence of significant stenosis.

Mixed aortic valve disease

Pulse, blood pressure, apex examination and the character of the murmur may be used to determine which is dominant (Table 3.15). Consider also the possibility of a prosthetic aortic valve with an ejection systolic flow murmur and an early diastolic murmur suggesting a paravalvular leak.

Interpretation

Confirm the diagnosis

Use Tables 3.14 and 3.15 to determine likely dominant lesions but tell the examiners that echocardiography is needed to resolve the issue.

Table 3.14 Determination of predominant mitral valve abnormality

	Mitral stenosis	Mitral regurgitation
Pulse	Small volume	Normal volume or hyperdynamic
Blood pressure	Usually unhelpful	Usually unhelpful
Apex	Not displaced	Displaced
	Tapping	Thrusting
Heart sounds	Loud S1	Soft or absent S1 +/− S3
Murmur	Rumbling mid-diastolic	Blowing pansystolic

Table 3.15 Determination of predominant aortic valve abnormality

	Aortic stenosis	Aortic regurgitation
Pulse	Slow rising	Collapsing
Blood pressure	Narrow pulse pressure with low systolic pressure	Wide pulse pressure with high systolic pressure
Apex	Not displaced	Displaced
	Heaving	Thrusting
Heart sounds	Soft / absent S2	Quiet S1
		Normal / soft S2
Murmur	Harsh 'sawing wood' ejection systolic	Whispering early diastolic
	Thrill	

What to do next – consider causes

Causes of mitral stenosis, mitral regurgitation, aortic stenosis and aortic regurgitation are described in separate cases.

Consider severity / decompensation / complications

Signs of severe mitral stenosis, mitral regurgitation, aortic stenosis and aortic regurgitation are described in separate cases.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic until too late) and consider fitness for surgery.

Discussion

Questions about valve lesions are answered in cases on specific valve lesions.

CASE 3.8 MITRAL VALVE PROLAPSE

Instruction

This 30-year-old woman is thought to have a heart murmur. Please examine her cardiovascular system and report your findings.

Recognition

Signs of mitral valve prolapse are shown in Figure 3.11.

Interpretation

Confirm the diagnosis

Tell the examiners that you would like to perform dynamic auscultation (Table 3.16).

What to do next – consider causes

Mitral valve prolapse is common, affecting between 2% and 10% of the population. Tell the examiners that occasionally it may be associated with:

- Marfan's syndrome (tall, long extremities with arm span > height, arachnodactyly, high arched palate)
- Rheumatic heart disease
- An ostium secundum atrial septal defect
- Ehlers–Danlos syndrome
- Ebstein's anomaly
- Systemic lupus erythematosus.

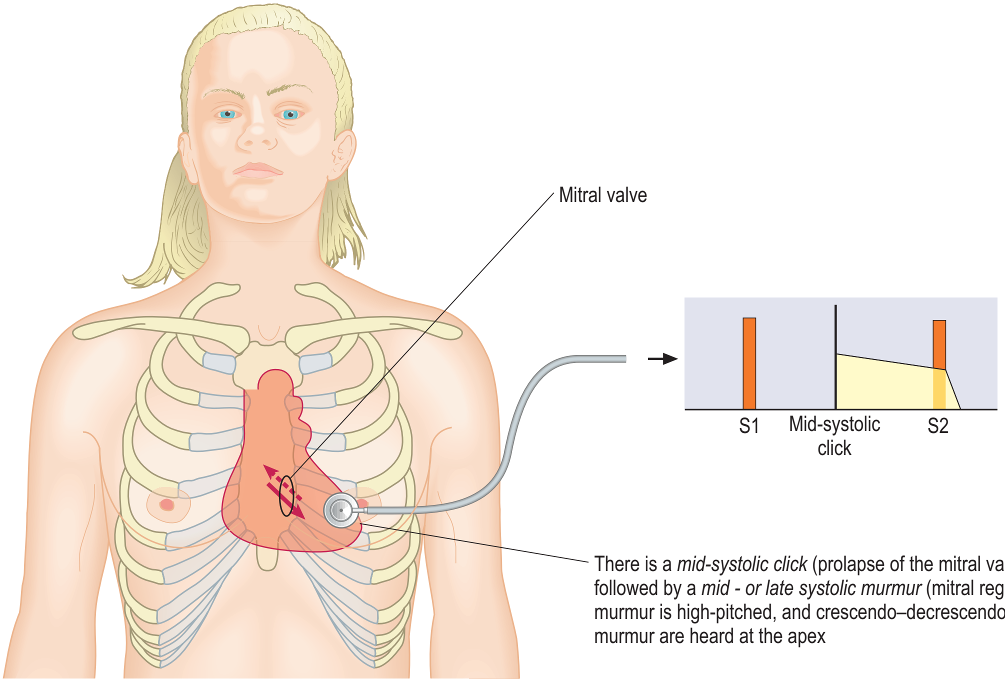
Consider severity / decompensation / complications

Complications of mitral valve prolapse include:

- Severe mitral regurgitation
- Arrhythmias
- Atypical chest pain
- Transient ischaemic attacks or strokes

Table 3.16 Effect of dynamic manoeuvres on mitral valve prolapse murmur

Manoeuvre		Effect
Valsalva Reduces venous return		Longer and louder and follows earlier click because prolapse enhanced when heart underfilled
Position	**Standing** Reduces venous return	Longer and louder and follows earlier click
	Squatting or passive leg raising Enhances venous return	Softer and shorter and follows later click
Exercise	**Isometric (hand grip)** Enhances venous return	Softer and shorter and follows later click



There is a *mid-systolic click* (prolapse of the mitral valve into the left atrium) followed by a *mid - or late systolic murmur* (mitral regurgitation). The murmur is high-pitched, and crescendo–decrescendo. Both click and murmur are heard at the apex

Figure 3.11 Mitral valve prolapse.

- Infective endocarditis (usually only if associated mitral regurgitation)
- Sudden cardiac death.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic) and consider the need for surgery.

Discussion

What is the pathophysiology of mitral valve prolapse?

Mitral valve prolapse encompasses a spectrum of severities. Some patients have 'floppy' but non-prolapsing mitral valves. In cases of prolapse, the posterior leaflet is usually more affected, but both can prolapse. The mid-systolic click may be produced by the sudden tensing of the slack, elongated chordae tendinae or by the prolapsed leaflet at maximum excursion. Ruptured chordae tendinae and progressive annular dilatation may contribute to the subsequent regurgitation and eventually mitral valve prolapse may be extinguished by the signs of severe mitral regurgitation. Some patients have a click and no murmur and some patients have a murmur and no click.

CASE 3.9 PROSTHETIC VALVES

Instruction

Please examine this woman's cardiovascular system and discuss your findings.

Recognition

Mitral valve prosthesis

There is a *midline sternotomy scar*. There is a *metallic S1 click* representing closure of the prosthesis, a *metallic opening snap* in diastole and a *normal S2*. Systolic murmurs are common and do not necessarily indicate valve dysfunction.

Aortic valve prosthesis

There is a *midline sternotomy scar*. *S1 is normal* and is followed by an *ejection click* (often synchronous with S1) representing opening of the prosthesis, an *ejection systolic murmur* and an *S2 click* representing closure of the prosthesis. An early diastolic murmur and collapsing pulse imply a leaking prosthetic aortic valve.

Mitral and aortic valve prostheses

Both mitral and aortic valves may be prosthetic.

Interpretation

Confirm the diagnosis

The click of a mechanical valve is unmistakeable.

What to do next – consider causes

The most common reason for valve replacement is valve degeneration. Other causes include congenital heart disease and infective endocarditis.

Consider severity / decompensation / complications

Look for splinter haemorrhages or other signs of infective endocarditis. Listen for regurgitation. List some complications of valve replacement to the examiners (Box 3.13).

Consider function

Tell the examiners that a normal functioning valve should not give rise to symptoms.

Discussion

What types of prosthetic valve are available, and what are the pros and cons?

The notion that mechanical valves are for younger people and bioprosthetic valves for older people is less apt these days, as valves and techniques have changed and considerations are many and individually determined.

Mechanical valves

These are more durable than bioprosthetic valves, but more thrombogenic and require anticoagulation. Three designs are available. Caged-ball valves (e.g. Starr–Edwards) were the first and are highly durable but have significant problems with haemolysis, thrombogenesis and regurgitation. Titling disc valves (e.g. retired Björk–Shiley) improved the haemodynamic profile with reduced thrombogenic potential in the aortic position. Bi-leaflet

Box 3.13 **Complications of valve surgery**

Early (postoperative)

- Death
- Stroke
- Myocardial infarction
- Haemorrhage
- Infection
- Heart block
- Atrial fibrillation (common)

Late

- Structural valve deterioration (bioprosthetic)
- Thromboembolic
- Paravalvular leak or valve regurgitation

valves (e.g. St Jude) are now invariably used, with a leaflet hinge mechanism. These valves enable 'washing' of the leaflets by allowing haemodynamically insignificant regurgitation across the valve during diastole. Most modern mechanical valves have 98% freedom from degeneration at 10 years.

Bioprosthetic valve

These are less durable but are preferred in some circumstances, particularly because anticoagulation is not needed. Three types of bioprosthesis are available. Xenografts are the most common, porcine or bovine with or without a wire or polyacetal stent. They are prone to degeneration, affecting around 5% of valves in the aortic position at 5 years and 30% at 10 years, owing to calcification. Homografts (allografts) and autografts are less commonly used, the latter sometimes used to replace a diseased pulmonary valve with an aortic valve, which lasts longer in the pulmonary position because of lower pressure; but double-valve surgery is needed for single-valve pathology.

Which factors help to determine the choice of valve?

Aortic valve

Generally patients over 75 years of age receive a xenograft. These close against the lower diastolic pressure of the aorta and are more durable than in the mitral position. In patients under 50 years of age a homograft or autograft might sometimes be considered because they are more durable than xenografts and avoid the need for anticoagulation. Other patients usually receive mechanical valves unless there are contraindications to anticoagulation such as liver disease, haemorrhagic stroke, frequent falls or pregnancy.

Mitral valve

Preservation and repair of native valves is generally preferable to mitral valve replacement. Xenografts are avoided except in very elderly patients with limited life expectancy because of the need for durability.

Why might prosthetic valves become regurgitant?

Degeneration and endocarditis are the usual suspects. A trivial paravalvular leak is invariable with any prosthetic valve.

CASE 3.10 PERMANENT PACEMAKER AND CARDIAC DEVICE THERAPIES

Instruction

Please examine this man's cardiovascular system and discuss your findings.

Recognition

There is a permanent pacemaker/cardiac device *in situ* (Fig. 3.12).

Interpretation

Confirm the diagnosis

There are three broad types of cardiac device therapy (Box 3.14).

What to do next – consider causes

The indications for a permanent pacemaker and other implantable cardiac devices are described below. Permanent pacemakers are most commonly inserted when ischaemic or degenerative conducting pathways give rise to sinus pauses causing presyncope or syncope.

Consider severity/decompensation/complications

The patient will likely be well. Common features of all are insertion via a subclavian vein, a pulse generator and intracardiac electrodes. Thus complications common to all include the following:

- Subclavian vein insertion complications (pneumothorax, thrombosis)
- Pulse generator pocket complications (infection, erosion through skin); pulse generator complications (battery depletion, inappropriate programming – e.g.

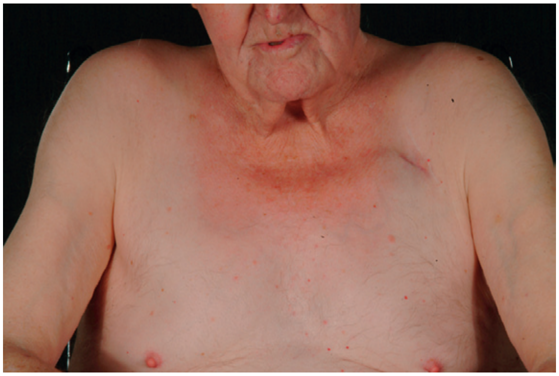


Figure 3.12 Permanent pacemaker.

Box 3.14 **Cardiac device therapies**

- Anti-bradycardia pacemakers
- Cardiac resynchronisation therapy pacemakers – Case 2.10 (Heart failure)
- Implantable cardiac defibrillators – Case 2.10 (Heart failure) describes use in ischaemic cardiomyopathy and Case 2.11 (Palpitations and arrhythmias) describes use in other conditions

from external electromagnetic interference but now uncommon because of better insulation, runaway)
- Intracardiac electrode complications (endocarditis, displacement/perforation, failure to pace or sense or inhibit, e.g. pacing spike but no QRS complex).

Consider function

This depends on the underlying cause. Pacemaker syndrome, now uncommon, arises when retrograde conduction produces atrial contraction against a closed atrioventricular valve; this leads to decreased ventricular filling and decreased cardiac output with presyncopal symptoms.

Discussion

What kinds of pacing do you know of?

There is a code to pacing with three letters: the first refers to the paced chamber (atrium A, ventricle V or dual D), the second the sensed chamber (A, V or D) and the third the mode of pacing (inhibited I, triggered T or dual D). All modes may include R. R implies rate responsive – movement is sensed and the pacing rate increases if the pacer 'thinks' the patient is exercising.

VVI pacing via a temporary pacing wire placed into the right ventricle after inferior myocardial infarction is commonplace. A single electrode senses the QRS complex, a single electrode paces the QRS complex, and pacing is inhibited if a QRS complex is sensed. In other words, this is on-demand pacing only. The electrocardiogram (ECG) shows pacing spikes followed by broad QRS complexes when atrial activity has not occurred, and there is complete P wave dissociation because the atria are neither sensed nor stimulated. The operator may adjust the rate at which pacing is triggered. If the heart rate falls from 60 to 59 and the pacer is set to trigger at < 60, V will take over; thus a small change in intrinsic heart rate can result in a large change physiologically – if the patient's intrinsic heart rate happens to be around 60, continual switching in and out of pacing can be very uncomfortable and VVI pacing can produce cannon waves.

AAI pacing involves pacing the right atrium and is inhibited if P waves are sensed. It is used in sick sinus syndrome and requires normal conducting pathways distal to the atrioventricular node. The advantage is that it provides the physiological atrial 'kick' or systole. The ECG shows atrial pacing spikes followed by normal narrow QRS complexes.

DDD dual chamber pacing is more physiological and in patients with heart block and P wave activity has largely superseded single chamber pacing.

What do you understand by the term overdrive pacing for tachyarrhythmias?

Underdrive pacing was used in early pacemakers to treat supraventricular tachycardia and ventricular tachycardia (VT). Extra stimuli were introduced at a constant interval but slower rate than the tachycardia, until one arose during the critical period to terminate it. Because of a lack of sensing of the underlying tachycardia, there was a risk of a paced beat falling on a T wave producing VT or ventricular fibrillation or converting atrial tachycardias into atrial fibrillation. It has been superseded by overdrive pacing. Radiofrequency ablation has reduced some need for implantable devices to terminate some arrhythmias such as paroxysmal atrial fibrillation, although pacing is commonly used for atrial as well as ventricular arrhythmias. Any device capable of pace termination of VT must also have defibrillatory capacity.

CASE 3.11 INFECTIVE ENDOCARDITIS

Instruction

Please examine this woman's hands and then auscultate the heart. Discuss your proposed further assessment and management.

Recognition

Peripheral signs include *anaemia*, *clubbing*, *Janeway lesions* (non-tender red palmar or plantar haemorrhagic macules or pustules), *Osler's nodes* (tender nodules of the finger and toe pulps), *splinter haemorrhages*, *subconjunctival haemorrhages* and areas of *digital infarction*. A *murmur* is present (state location and describe).

Janeway lesions are the result of septic embolisation and Osler's nodes of immunological activity and both are less common peripheral stigmata these days because infective endocarditis tends to present at an earlier stage. Vasculitic phenomena (Fig. 3.13) such as splinter haemorrhages are more common; splinter haemorrhages appear as red lines for the first two or three days and are brown thereafter.

Interpretation

Confirm the diagnosis

Clinical suspicion

Some circumstances in which infective endocarditis should always be considered are the presence of staphylococcal or streptococcal (or enterococcal) bacteraemia, candidaemia, fever, raised inflammatory markers, embolic phenomena and vertebral infection or discitis (30% of cases are associated with infective endocarditis). The Duke criteria (Duke University of North Carolina) are widely used for diagnosing infective endocarditis (Table 3.17).

Blood cultures and echocardiography

Tell the examiners that diagnosis is confirmed by positive blood cultures and transthoracic echocardiography (TTE) or transoesophageal echocardiography (TOE) evidence of

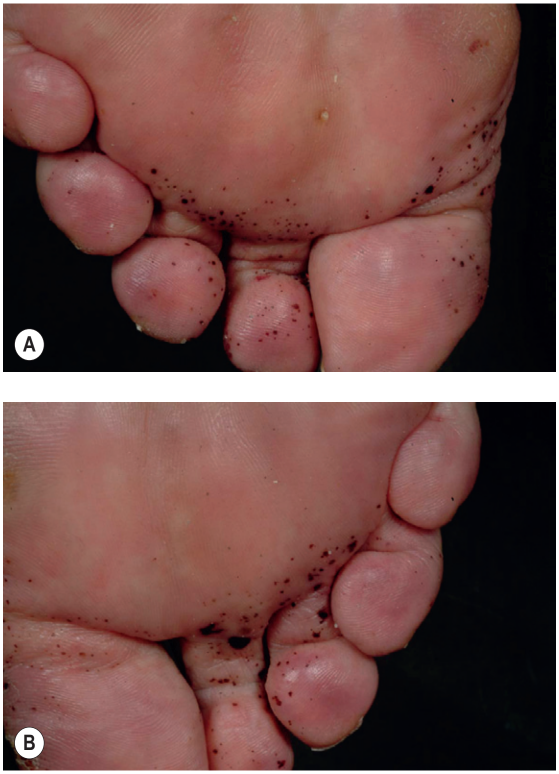


Figure 3.13 (A, B) Vasculitic rash.

vegetation. Blood cultures are positive in over 90% of patients cultured from two sites, provided an antibiotic has not been administered. Serological assays and polymerase chain reaction testing may aid diagnosis when organisms are difficult to culture. TTE is indicated where there is clinical suspicion followed by TOE if there is a prosthetic valve or cardiac device, the TTE is of poor quality, if the TTE is positive or if the TTE is negative but high clinical suspicion remains.

What to do next – consider causes / assess other systems

Tell the examiners you would:

- Ask about predisposing factors, especially valvular or congenital heart disease or valve prostheses.
- Look for fever, clubbing and splenomegaly – because of the generalised activation of the reticuloendothelial system in subacute bacterial endocarditis. Note that in right-sided endocarditis (common with intravenous drug use), peripheral stigmata will not occur.
- Ask whether there is leucocytosis or if inflammatory markers are raised (not always, e.g. early in disease, fungi).

Box 3.15 **Complications of infective endocarditis**

- Valve destruction and heart failure; changing murmurs are common, indicating change in size of a vegetation or embolisation of part thereof, or worsening valve destruction
- Embolic complications: these affect 20–50% of patients and are often the presenting feature – up to two-thirds are neurological complications (e.g. stroke, cerebral metastatic abscess formation, mycotic aneurysms – septic embolisation of vegetations to a vessel wall, more common in delayed presentation) but other sites of embolic spread include the lungs, spleen, kidneys, gut, liver, skin (Janeway lesions)
- Disseminated sepsis and multi-organ failure
- Intracardiac abscess formation, e.g. aortic root abscess
- Pulmonary emboli (common in intravenous drug users, seeding from tricuspid vegetations)
- Circulating immune complexes causing glomerulonephritis

Consider severity / decompensation / complications

Tell the examiners of possible complications (Box 3.15). Infective endocarditis in-hospital mortality is high, at 10–26%.

Consider function

This is dependent on symptoms and the underlying cause.

Discussion

How does infective endocarditis arise?

Infective endocarditis arises when trauma or ulceration to the valvular endothelial surface promotes bacterial adherence by one of two mechanisms. Firstly, it could induce a valve thrombus when subendothelial components are in direct contact with blood; pathogens arising in transient bacteraemia bind avidly to this potential culture medium and subsequent cytokine activation by monocytes progressively enlarges the subsequent vegetation. Secondly, local inflammation promotes the cellular expression of transmembrane proteins that bind fibronectin; pathogens such as *Staphylococcus aureus* carry fibronectin-binding protein on their surface and so can adhere to the inflammatory focus. Staphylococcal endocarditis often occurs on previously normal valves, probably induced by microulcerations.

Valve trauma is more likely in the presence of a structurally abnormal valve or where there is turbulent blood flow. High shear stress is more likely in the region of the mitral and aortic valves, the tricuspid and pulmonary valves being colonised with decreased frequency, respectively. Once seeded with infection, 'vegetations' tend to appear downstream of the jet of blood flow on the low-pressure side of the valve (e.g. the ventricular side of the aortic valve) normally close to the closure line of the leaflet.

Table 3.17 Modified Duke criteria for diagnosing infective endocarditis

Major	Microbiological If infective endocarditis likely and haemodynamic compromise, treatment should start immediately after three sets of blood cultures at separate sites; otherwise, diagnostic work-up should pre-empt treatment	Typical micro-organism isolated from two separate blood cultures: viridans streptococci, *Streptococcus bovis*, HACEK group (see text), *Staphylococcus aureus* or community-acquired enterococcal bacteraemia without a primary focus	
		Micro-organism consistent with, but less specific for, infective endocarditis isolated from persistently positive blood cultures	
		Single positive blood culture for *Coxiella burnetii* or appropriate serology for *C. burnetii*, *Bartonella* species or *Chlamydia psittaci*	
		Positive molecular assays for specific gene targets	
	Evidence of endocardial involvement	Positive echocardiogram showing oscillating structures, abscess formation or new valvular regurgitation, or dehiscence of prosthetic valves	
Minor	Predisposition (includes predisposing heart disease and injection drug use)	High risk	Previous infective endocarditis Aortic valve disease Rheumatic heart disease Prosthetic valve Aortic coarctation Acyanotic congenital heart disease
		Moderate risk	Mitral valve prolapse with mitral regurgitation or leaflet thickening Isolated mitral stenosis Tricuspid valve disease Pulmonary stenosis Hypertrophic cardiomyopathy
		Low or no risk	Secundum atrial septal defect Ischaemic heart disease Previous coronary artery bypass grafting Mitral valve prolapse with thin leaflets in absence of mitral regurgitation
	Fever	> 38°C	
	Vascular phenomena	e.g. major emboli, splenomegaly, clubbing, splinter haemorrhages, petechiae or purpura	
	Immunological phenomena	e.g. glomerulonephritis, Osler's nodes, Roth's spots, positive rheumatoid factor	
	Microbiological findings	Positive blood cultures that do not meet major criteria	
Pathological	Positive histology or microbiology of autopsy or cardiac surgery material		

Definite infective endocarditis is diagnosed (sensitivity 80% and specificity 90%) by positive pathological criteria OR two major criteria OR one major and two minor criteria OR five minor criteria; one major and one minor criterion OR three or four minor criteria should probably be treated as infective endocarditis with the patient under close review.

What is a vegetation?

A vegetation is a collection of platelets, fibrin, micro-organisms and inflammatory cells.

How does the bacteraemia that causes infective endocarditis arise?

Bacteraemia is usually part of a nosocomial or iatrogenic infection. Areas more heavily colonised with bacteria (mouth, gastrointestinal tract) are more likely to predispose to bacteraemia. Bacteraemia can occur with mild trauma, dental interventions being a notable, although hitherto overemphasised, source, whilst cumulative risks from routine tooth brushing may be underestimated. Intravenous drug users are at particularly high risk.

Which valve lesions are susceptible to infective endocarditis?

These are any valve disease (commonly degenerative valve sclerosis, mitral valve prolapse with regurgitation, prostheses or damage from previous endocarditis, but historically rheumatic), hypertrophic cardiomyopathy or congenital heart disease. Atrial septal defect endocarditis is rare.

How is the epidemiology of infective endocarditis changing?

Infective endocarditis increasingly affects older people, those with valvular heart disease, those with cardiac devices and health-care-associated states (within 1 month). Local knowledge is vital, since the type of infective endocarditis and organisms are determined by locality (e.g. local intravenous drug use or a local dialysis unit may influence organism type, culture-negative organisms are more likely in North Africa).

Which organisms cause endocarditis?

The profile of organisms varies locally and changes over time. The two main organisms remain staphylococci and streptococci (or *Enterococcus*).

Native valve endocarditis

This has tended to be the caused by *viridans* streptococci, which colonise the oral cavity, lower gastrointestinal tract and genitourinary tract, but may also be the result of staphylococci, Gram-negative bacilli (e.g. *Enterococcus* via bowel pathology or urinary tract infection) or organisms that are notoriously culture negative. Staphylococci, especially *S. aureus*, are now surpassing *viridans* streptococci as the most common cause of endocarditis. *Staphylococcus lugdunensis* is a less common but particularly destructive cause of endocarditis, surviving patients usually needing valve replacement. The most common streptococci continue to be *Strep. sanguis*, *Strep. bovis*, *Strep. mutans* and *Strep. mitis*. *Streptococcus bovis* is especially common in older people with colonic lesions. Native valve endocarditis is more common in men, with an increasing incidence in older people as valves degenerate and nosocomial infection becomes more likely.

Prosthetic valve endocarditis

This accounts for around 10–15% of infective endocarditis. It may occur early, mostly caused by coagulase-negative staphylococci, including *S. aureus* and *S. epidermidis*, or late with a similar organism profile to native valve disease.

What are the causes of culture-negative infective endocarditis?

This may be due to:

- Antibiotic use (most cases)
- Organisms that are notoriously difficult to culture, e.g. the HACEK group of organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species), *Brucella* and fungi
- Organisms that tend never to culture, including *Coxiella burnettii* (Q fever), *Bartonella* (trench fever, louse-borne) and some fungi and yeasts (*Candida*, *Aspergillus*, *Histoplasma*, *Cryptococcus*).

How do subacute bacterial endocarditis (SBE) and acute bacterial endocarditis differ?

The term infective endocarditis is generally replacing these two terms. *Viridans* streptococci grow slowly and have tended to be associated with SBE, presenting with fevers and weight loss. *S. aureus* tends to cause acute bacterial endocarditis and is common in patients with prosthetic heart valves and in intravenous drug users; acute fever is more likely, as are abscess formation, valve destruction and metastatic infection causing brain abscesses and intracerebral haemorrhage. Fungi and *S. aureus* carry the highest mortality.

What are the management principles in infective endocarditis?

Teamwork is essential, with close liaison with cardiology and microbiology services.

Diagnosis is frequently difficult, particularly in patients with prosthetic valves, intracardiac devices, or blood-culture-negative disease. The Duke criteria are useful for classification, but do not replace clinical judgement. Echocardiography (TTE and TOE) and blood cultures are the cornerstone of diagnosis and should be performed in the majority of cases of suspected or definite disease.

Prognostic assessment is crucial in choosing the optimal therapeutic strategy, performed using clinical, microbiological and echocardiographic parameters.

Prolonged therapy with a combination of high-dose bactericidal drugs intravenously is the basis of treatment. Drug treatment of prosthetic valve and device therapy endocarditis should last longer (at least 6 weeks) than that of native valve endocarditis (2–6 weeks).

List some indications for urgent surgery in infective endocarditis

The three main complications indicating early surgery are heart failure, uncontrolled infection and embolic events:

- Heart failure is the most frequent and severe complication and unless severe comorbidity exists is an indication for early surgery.
- Uncontrolled infection is most frequently related to perivalvular extension (abscesses or fistulae) or ‘difficult-to-treat’ organisms and unless severe comorbidity exists is an indication for early surgery.
- Embolism is very frequent, complicating 20–50% of cases of infective endocarditis. The risk of embolism is related to the size and mobility of the vegetation and is highest during the first 2 weeks of antibiotic therapy. Neurological events develop in 20–40% of all patients and are mainly the consequence of embolism. After an ischaemic stroke cardiac surgery is not contraindicated unless the neurological prognosis is judged to be poor. Large vegetations with high embolic potential (e.g. > 10 mm) are also considered for surgery.

Those at high risk might also be considered for surgery, such as those with left-sided infective endocarditis, a prosthetic valve, a cardiac device or a vegetation.

When should antibiotic prophylaxis be considered?

Antibiotic prophylaxis is recommended for patients undergoing high-risk dental procedures. Many cardiologists consider dental prophylaxis essential, against advice in the National Institute for Health and Clinical Excellence guidelines, which suggest that bacteraemia occurs in simple dental hygiene without provoking infective endocarditis and that the evidence for prophylaxis is insufficient. Good oral hygiene is very important. Guidelines do not advocate prophylaxis for gastrointestinal, genitourinary, respiratory or gynaecological procedures.

CASE 3.12 CONGENITAL ACYANOTIC HEART DISEASE

Instruction

This man has a congenital heart murmur. Please examine his cardiovascular system and report your findings.

Recognition

At birth, pulmonary vascular resistance falls as the lungs inflate and more blood flows through them. Left atrial blood flow increases causing closure of the foramen ovale (a connection between the atria). The ductus arteriosus usually closes within 24 hours of birth. Congenital heart disease is common and often multiple abnormalities occur. It may be acyanotic or cyanotic (Table 3.18).

Ventricular septal defect (VSD)

There is a *pansystolic murmur* and often a *thrill* at the *left sternal edge*. This represents blood flowing from the high-pressure left ventricle to the low-pressure right ventricle. There may be a *mid-diastolic flow murmur* at the apex and a *right ventricular heave* due to right ventricular volume overload.

Atrial septal defect (ASD)

Ostium secundum atrial septal defect

This is the commonest ASD, presenting in childhood or adulthood. There is a *right ventricular heave*, reflecting right ventricular overload with hypertrophy. Left-to-right shunting causes increased flow across the pulmonary valve and results in an *ejection systolic murmur* in the *pulmonary area* (left second/third intercostal space). S2 (A2–P2) is *widely split*, because of delayed pulmonary valve closure, and *fixed*. ASDs are often large and under low pressure with little turbulence, and it is a common misconception that the murmur is due to the ASD itself. There may also be a *mid-diastolic flow murmur* across the *tricuspid valve* (heard best at the left fourth intercostal space).

ASD is illustrated in Figure 3.14.

Ostium primum ASD

This is less common and usually presents in childhood with associated mitral regurgitation.

Patent ductus arteriosus

Small defect

There is a *loud continuous 'machinery' murmur*. This is due to increased blood flow through the lungs (pulmonary arteriovenous fistulae also sound like this). The continuous murmur is *pansystolic/early diastolic* and heard best over the *left upper sternal edge and clavicle*. There may be an associated *thrill*.

Large defect

There is a *collapsing pulse* (aortic diastolic run-off), and a *mid-diastolic tricuspid flow murmur* due to right-sided heart overload.

Aortic coarctation

There are *large-volume radial pulses* (left may be weaker) and there is vigorous *carotid pulsation* (although aortic regurgitation is a much more common cause). Blood pressure would be lower in the legs than arms and there is *radio-femoral delay* – the femoral pulse is delayed and of small volume. There is an *ejection systolic murmur* (which may be loud posteriorly but not audible anteriorly). There are *bruits* over the *scapulae, anterior axillary areas and left sternal edge* (internal mammary artery). *Collateral* blood vessels may be visible when the patient sits forward (Fig. 3.15).

Table 3.18 Congenital heart disease

Acyanotic (majority of congenital heart disease)		**Cyanotic**
With left-to-right shunt (high to low pressure unless shunt reversal occurs)	Without shunt	Always right-to-left shunt
Ventricular septal defect Atrial septal defect Patent ductus arteriosus and other aorto-pulmonary shunts Aortic root to right heart shunts Multilevel shunts	Aortic coarctation (narrowing just below the origin of the left subclavian artery) Congenital left heart inflow abnormalities, e.g. pulmonary vein stenosis Congenital mitral stenosis Congenital mitral regurgitation Congenital aortic stenosis Ebstein's anomaly Congenital pulmonary stenosis Congenital pulmonary regurgitation	Fallot's tetralogy Transposition of the great arteries, which presents at birth Eisenmenger's syndrome

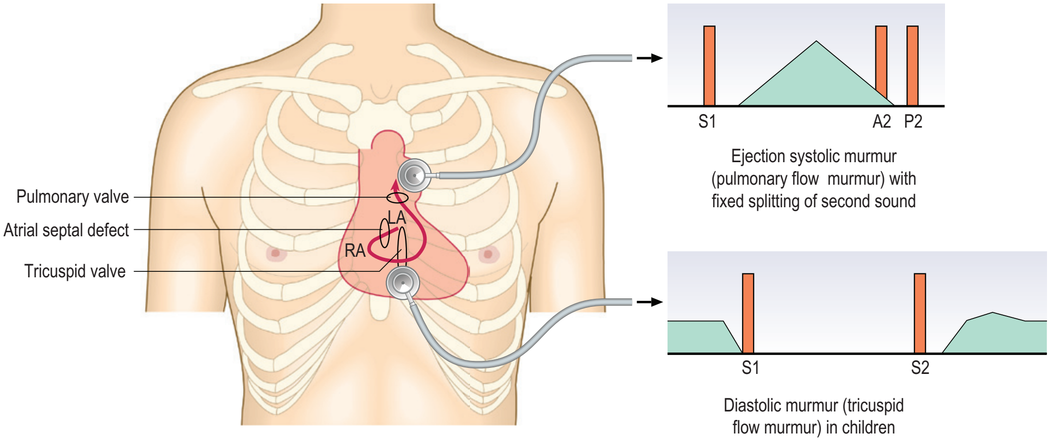

Pulmonary valve
Atrial septal defect
Tricuspid valve
LA
RA
S1
A2
P2
Ejection systolic murmur (pulmonary flow murmur) with fixed splitting of second sound
S1
S2
Diastolic murmur (tricuspid flow murmur) in children

Figure 3.14 Atrial septal defect. LA, left atrium; RA, right atrium.

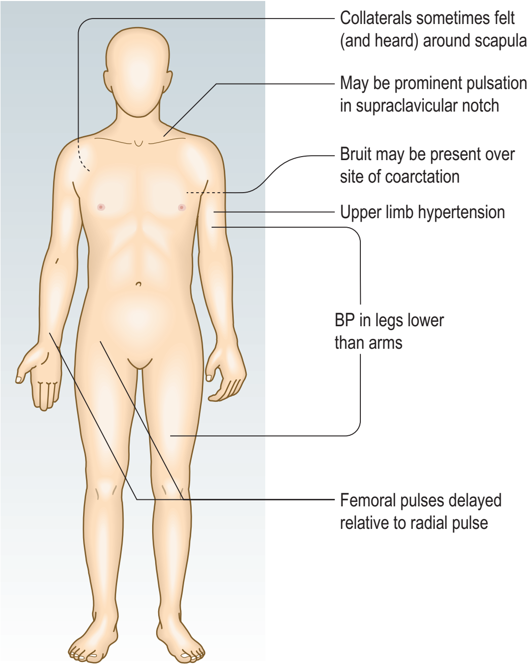

Collaterals sometimes felt (and heard) around scapula
May be prominent pulsation in supraclavicular notch
Bruit may be present over site of coarctation
Upper limb hypertension
BP in legs lower than arms
Femoral pulses delayed relative to radial pulse

Figure 3.15 Features of coarctation of the aorta. BP, blood pressure.

Interpretation

Confirm the diagnosis

Tell the examiners that further investigations include electrocardiogram (ECG), chest X-ray, echocardiography and cardiac catheterisation (Table 3.19).

What to do next – consider causes / assess other systems

Tell the examiners likely causes and associations (Table 3.20).

Consider severity / decompensation / complications

Tell the examiners of important potential complications (Table 3.21).

Consider function

The patient might look well or chronically unwell (e.g. underweight, cyanosed, clubbed).

Discussion

Where types of VSD are there?

VSDs occur at four common sites:

- Membranous septum ('infracristal') – the commonest site, just behind the medial papillary muscle of the tricuspid valve which may oppose it and help it to close spontaneously
- Muscular septum – variable site and may be multiple (acquired VSD after septal infarction is usually the 'Swiss cheese' type)
- Infundibular ('supracristal') – a high VSD just beneath the pulmonary valve and below the right coronary cusp of the aortic valve; the latter may be inadequately supported and prolapse, causing aortic regurgitation; an infundibular VSD may also be associated with malalignment of the infundibular septum, e.g. with shift of the septum to the right as in Fallot's tetralogy or shift of the septum to the left with a double outlet left ventricle and subaortic stenosis
- Posterior (atrioventricular defect) – a paratricuspid defect.

Table 3.19 Diagnosing acyanotic congenital heart disease

Ventricular septal defect	Atrial septal defect	Patent ductus arteriosus	Aortic coarctation
ECG may show signs of right or left ventricular hypertrophy Chest X-ray may show enlarged pulmonary arteries Echocardiography and cardiac catheterisation would confirm anatomical abnormalities, pressures and oxygen saturations	ECG differentiates between OS and OP ASDs – OS ASDs tend to cause right bundle branch block and right axis deviation and OP ASDs right bundle branch block and left axis deviation Echocardiography confirms suspicions	Diagnosed by echocardiography	ECG may show left ventricular hypertrophy Chest X-ray may show rib notching on the inferior surfaces of ribs due to tortuous arterial collaterals and there may be a 'figure 3' pattern resulting from an upper bulge (the left subclavian artery), a notch (representing coarctation) and a lower bulge (poststenotic dilatation) Thoracic imaging confirms suspicions

ASD, atrial septal defect; ECG, electrocardiogram; OP, ostium primum; OS, ostium secundum.

Table 3.20 Causes and associations in acyanotic congenital heart disease

Ventricular septal defect	Atrial septal defect	Patent ductus arteriosus	Aortic coarctation
Usually congenital Occasionally post-myocardial infarction	Holt–Oram syndrome: OS ASD + hypoplastic thumbs Lutembacher's syndrome: ASD + rheumatic mitral stenosis Usually isolated, however	Congenital	Usually idiopathic (more common males, commonly asymptomatic until adulthood and presenting at around the third decade with hypertension) Turner's syndrome

ASD, atrial septal defect; OS, ostium secundum.

Table 3.21 Complications in acyanotic congenital heart disease

Ventricular septal defect	Atrial septal defect	Patent ductus arteriosus	Aortic coarctation
Infective endocarditis Aortic regurgitation due to prolapse of right coronary cusp (5% of ventricular septal defects) Infundibular stenosis – right-sided heart failure Reversal of shunt and Eisenmenger's syndrome (cyanosis)	Infective endocarditis Atrial fibrillation Eisenmenger's syndrome (cyanosis)	Infective endocarditis Pulmonary hypertension Eisenmenger's syndrome (cyanosis)	Infective endocarditis Hypertension (may persist post surgery) Bicuspid aortic valve Cerebral aneurysms

How are VSDs treated?

Small defects often close spontaneously in childhood, especially membranous VSDs. Infundibular VSDs do not close spontaneously. VSDs should be assessed regularly for complications and closed before the onset of Eisenmenger's syndrome. Indications for surgery include recurrent endocarditis, aortic regurgitation or volume overload, and acute septal rupture.

When should surgery be contemplated for an ASD?

OS ASDs have traditionally been closed in or before the third decade, but recent thinking is that there may be less gained from surgery in asymptomatic adults.

CASE 3.13 CYANOTIC HEART DISEASE

Instruction

This young woman has a congenital heart murmur. Please examine her cardiovascular system and report your findings.

Recognition

There is *cyanosis, clubbing, a right ventricular heave* and an *intense pulmonary ejection systolic murmur* at the *left sternal edge* with an associated *thrill*.

Interpretation

Confirm the diagnosis

Tell the examiners that further investigations include electrocardiogram (ECG), chest X-ray, echocardiography and cardiac catheterisation. In Fallot's tetralogy the ECG usually shows sinus rhythm, right axis deviation and right ventricular hypertrophy with right bundle branch block and the chest X-ray a classic coeur en sabot (heart in a boot) shape.

What to do next – consider causes

Cyanotic congenital heart disease may be due to Eisenmenger's syndrome or primary cyanotic congenital heart disease. Transposition of the great arteries is managed at birth but Fallot's tetralogy is, occasionally, not detected until the second or third decade, especially in people from countries with poorly resourced health-care. The complete syndrome (Table 3.18) comprises:

- Ventricular septal defect with right-to-left shunt
- Aorta overriding septal defect
- Pulmonary stenosis (resulting in diversion of right ventricular blood straight into the aorta)
- Right ventricular hypertrophy.

Consider severity / decompensation / complications

Eisenmenger's syndrome or primary cyanotic congenital heart disease represents a decompensated situation. Other complications of Fallot's tetralogy include poor growth, infective endocarditis and cerebral abscesses (absence of lung filter with left-to-right shunt).

Consider function

The patient might look well or chronically unwell (e.g. underweight, cyanosed, clubbed).

Discussion

What is Eisenmenger's syndrome?

Longstanding right-sided heart overload leads to pulmonary hypertension and reversal of the left-to-right shunt (Eisenmenger's syndrome). It leads to clubbing and central cyanosis and the progressive backward pressure consequences of pulmonary hypertension.

How is Fallot's tetralogy treated?

Treatments include total correction or Blalock–Taussig shunting in which the left subclavian artery is anastomosed to the left pulmonary artery to increase pulmonary blood flow.

CASE 3.14 HYPERTROPHIC (OBSTRUCTIVE) CARDIOMYOPATHY

Instruction

This 35-year-old man is thought to have a heart murmur. Please examine his cardiovascular system and report your findings.

Recognition

The *arterial pulse* is *jerky*. A sharp early rise of rapid ejection is followed by a late systolic phase as the dynamic obstruction supervenes (Fig. 3.16). Contrast this with the slow rising plateau pulse of aortic stenosis in which there is obstruction from the outset of systole (Table 3.22). There may be an *'a' wave* in the jugular venous pulse reflecting forceful atrial contraction of a hypertrophied atrium. There is a *double impulse at the apex*; this represents presystolic ventricular expansion from forceful atrial systole followed by a systolic left ventricular heave.

There may be a *fourth heart sound* due to atrial systole. A *late systolic ejection murmur at the left sternal edge* is due to dynamic obstruction (Fig. 3.16). This may be associated with a *systolic thrill at the left sternal edge* from turbulence. There may be an associated *pansystolic murmur at the apex* because mitral regurgitation is commonly associated. These findings suggest classic hypertrophic (obstructive) cardiomyopathy.

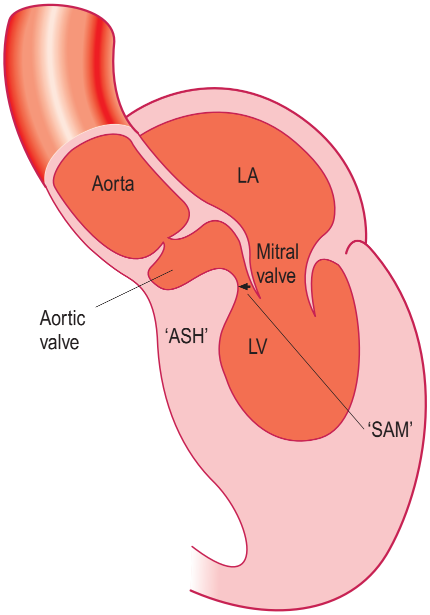


Figure 3.16 Asymmetrical septal hypertrophy (ASH) and systolic anterior motion (SAM) during systole. LA, left atrium, LV, left ventricle.

Table 3.22 Aortic stenosis versus hypertrophic (obstructive) cardiomyopathy

	Aortic stenosis	Hypertrophic (obstructive) cardiomyopathy
Carotid character	Slow rising	Bifid, jerky
Thrill	Upper right parasternal area	Lower left parasternal area
Ejection murmur	Characteristic up- and downstroke around mid-systole	Late systolic
Aortic early diastolic murmur	Often present	Rare
Effect of manoeuvres	Fixed murmur	Variable murmur

Box 3.16 **Symptoms of hypertophic cardiomyopathy**

- Asymptomatic
- Dyspnoea on exertion and symptoms of heart failure (diastolic dysfunction)
- Syncope or presyncope
- Palpitations (ventricular arrhythmias or atrial fibrillation common)
- Chest pain (in the absence of coronary atherosclerosis possibly microvascular dysfunction)
- Family history of syncope or sudden cardiac death
- Sudden cardiac death

Table 3.23 Effect of dynamic manoeuvres on murmur of hypertrophic (obstructive) cardiomyopathy

Manoeuvre		Effect
Valsalva Reduces venous return		Louder because reduced heart filling in diastole worsens the subsequent dynamic obstruction
Position	**Standing** Reduces venous return	Louder
	Squatting or passive leg raising Enhances venous return	Softer
Exercise	**Isometric (hand grip)** Enhances venous return	Softer

Interpretation

Confirm the diagnosis

Tell the examiners that you would ask about presenting symptoms, which may include any of those features in Box 3.16.

Tell the examiners that you would perform dynamic auscultation (Table 3.23).

What to do next – consider causes

Differentiate clinically an ejection systolic murmur due to hypertrophic (obstructive) cardiomyopathy and that due to aortic stenosis, the latter in a young person often due to a congenital biscuspid valve (Table 3.22).

Consider severity / decompensation / complications

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease with a wide spectrum of severity, and classic hypertrophic (obstructive) cardiomyopathy occupies only a small part (around 20%) of that spectrum. In HCM the myocardium is hypertrophied. Septal hypertrophy usually dominates and asymmetrical septal hypertrophy (ASH) is the characteristic pattern. There may, in addition to hypertrophy, be obstruction to the left ventricular outflow tract, which is dynamic, appearing in late systole – the hypertrophied septum distorts systolic movement of the left ventricle, and the most significant effect of this is systolic anterior movement of the anterior leaflet of the mitral valve (SAM); this results in mid- to late systolic subaortic obstruction due to mitral–septal contact and occurs at rest. There may also be diastolic dysfunction generated by stiffness of the hypertrophied ventricle.

Neither the severity of symptoms nor the left ventricular outflow gradient appears to correlate with prognosis as much as the underlying genetic mutation. However, outflow obstruction is associated with an increased risk of heart failure and sudden death. Features helpful in risk stratification are listed in Table 3.24.

Consider function

Tell the examiners you would establish the limitations provoked by symptoms (although often asymptomatic).

Discussion

What is meant by the term cardiomyopathy?

It generally refers to structural or functional myocardial disease in the absence of coronary disease, hypertension, valvular heart disease and congenital heart disease.

How common is HCM?

HCM is the most common familial genetic disease of the heart (1 : 500–1 : 1000) and the most common cause of sudden cardiac death in young people and athletes.

Table 3.24 Risk stratification of hypertrophic cardiomyopathy

Risk stratification	Features	Treatment
High	Family history of premature sudden death Extreme left ventricular hypertrophy (≥ 30 mm) in young patients Unexplained syncope in young patients Non-sustained ventricular tachycardia in patients aged ≤ 30 years Abnormal blood pressure response during exercise	Implantable cardioverter defibrillator for primary prevention if high-risk features or secondary prevention if sustained ventricular tachycardia or survived cardiac arrest
Low	Mild left ventricular hypertrophy (< 20 mm) and no risk factors	Medical therapy as required

What is the cause of HCM?

The genetic basis is a mutation in one of the genes coding for one of the myocardial contractile proteins – β-myosin heavy chain, cardiac myosin binding protein C, cardiac troponin I, troponin T, troponin C, α-tropomyosin, essential myosin light chain, regulatory myosin light chain, cardiac actin, α-myosin heavy chain, titin. A large number of mutations have been described, many with autosomal dominant inheritance, which share the basic histopathological consequence of myocardial fibre disarray. The major risk is arrhythmias resulting from the microarchitecture, such that the high proportion of people with hypertrophic cardiomyopathy without any obstructive features are at no less risk. Indeed, the greater determinant of risk is the underlying microarchitectural type. Some patients at risk even have no detectable hypertrophy.

Other cause of HCM with a systemic basis include glycogen and lysosomal storage diseases, diseases of fatty acid metabolism, mitochondrial cytopathies, athletic training, obesity, amyloidosis and genetic syndromes such as LEOPARD syndrome.

What might the electrocardiogram (ECG) show in HCM?

The ECG might show left ventricular hypertrophy, deep Q waves and conduction defects. It may be normal.

What might the echocardiogram show in HCM?

The echocardiogram might confirm ASH and SAM in hypertrophic (obstructive) cardiomyopathy, and there might be almost complete obliteration of the left ventricular cavity with a large outflow tract gradient.

Does magnetic resonance imaging (MRI) have a place in evaluating HCM?

MRI might detect hypertrophy that is confined to segments not identifiable on echocardiography.

How might the diagnosis be confirmed?

DNA analysis is now the definitive method for diagnosing many genetic diseases. However, HCM is caused by mutations in any one of the genes encoding proteins of the cardiac sarcomere and DNA analysis for diagnostic and screening purposes is not currently routine.

What are the treatment options for HCM?

Because of the relative rarity of HCM, randomised trials have not been conducted for treatment, and remain unlikely. Evidence is based on retrospective studies and clinical experience.

Medical treatment of heart failure

Dyspnoea on exertion in HCM is usually due to heart failure, and heart failure to a great extent reflects diastolic dysfunction because of the stiff left ventricle. Systolic function is usually well preserved. Medical treatment with beta blockers, verapamil or disopyramide improves exertional symptoms in patients with outflow obstruction but has not been shown to modify the clinical course. Diuretics are sometimes useful. Angiotensin-converting enzyme inhibitors must be exercised with caution because by reducing afterload may favour the development or worsening outflow obstruction. Atrial fibrillation develops in around 20% of patients with HCM and is rate controlled with beta blockers or verapamil and anticoagulation is usually indicated for thromboembolic prophylaxis.

Surgery

Patients with marked outflow obstruction (≥ 50 mmHg at rest) and severe symptoms (New York Heart Association class III or IV) unresponsive to medical therapy represent about 5% of patients with HCM and may be considered for surgical myectomy or alcohol septal ablation to relieve outflow obstruction.

Prevention of sudden cardiac death

A cardioverter defibrillator is the only effective treatment for prevention of sudden cardiac death. Indications include high-risk features (Table 3.24).

Is prophylaxis against infective endocarditis needed in HCM?

It is only indicated if there is obstruction at rest.

Does HCM increase pregnancy risk?

It generally carries little additional risk.

What lifestyle consequences are there for people with HCM?

Competitive sports associated with intense exertion or other strenuous physical activities should be avoided. People with a favourable clinical profile – asymptomatic, normal or only mildly increased left atrial dimension (< 45 mm), mild left ventricular hypertrophy (< 20 mm), no outflow obstruction at rest, no risk factors for sudden death – may participate in sports associated with mild or moderate physical activity.

What is the current screening practice for HCM?

Genetic screening is complex, as alluded to. Clinical screening of first-degree relatives is based on ECG and echocardiographic evaluation and is recommended every 2 years in children (when disease can change rapidly with growth) and every 5 years in adults.

What is dilated cardiomyopathy?

This refers to a dilated ventricle in the absence of ischaemic heart disease or abnormal loading (hypertension or valvular heart disease) and causes systolic dysfunction. Causes include alcohol, genetic disorders (Duchenne muscular dystrophy, myotonic dystrophy), nutritional deficiencies (e.g. thiamine), inflammatory causes (infection, toxic, eosinophilic) and drugs (e.g. anthracyclines).

What is restrictive cardiomyopathy?

Myocardial infiltration generally results in a degree of restriction. Amyloidosis and sarcoidosis are important causes. Haemochromatosis can cause dilation or restriction. Endomyocardial fibrosis is a chronic non-eosinophilic condition affecting young Africans and is difficult to treat. Loefler's endocarditis is an aggressive, eosinophilic cause of restriction. Diastolic dysfunction and conduction disturbances are the common manifestations of restrictive cardiomyopathy. Breathlessness, a positive Kussmaul's sign and other symptoms of heart failure without radiological evidence of cardiac enlargement should alert suspicion. The main differential diagnosis is constrictive pericarditis. Treatment is tricky.

What is myocarditis?

Myocarditis is relatively uncommon and caused by viruses (e.g. coxsackievirus), radiation, drugs, chemicals (e.g. lead) and Chagas' disease. It results in a dilated heart and heart failure, often in young adults. Sudden cardiac death is a possible complication and, as well as treating heart failure, the cause should be identified where possible and, at least in the early stages of the insult when sudden death appears especially risky, excessive exertion should be avoided. Around one-third of patients die or proceed to cardiac transplant, one-third have residual symptoms and one-third return to a normal life.

CASE 3.15 PERICARDIAL RUB AND PERICARDIAL DISEASE

Instruction

This patient is thought to have pericardial disease. Please examine her and discuss your diagnosis.

Recognition

Pericarditis

There may be a *pericardial rub*. This is a scratching or creaking sound, like snow underfoot or sometimes a little higher pitched like the creaking of timbers on an old ship. It is usually only apparent over an isolated area of cardiac auscultation and often changes or disappears with position, as does the patient's pain. It may be present at any stage in the cardiac cycle, but is often systolic.

Constrictive pericarditis

The signs of a constricted pericardium are similar to restrictive cardiomyopathy – both result in a *raised jugular venous pulse (JVP) with prominent x and y descents*, and *non-pulsatile hepatomegaly*. There may be a *pericardial knock*, representing an abrupt halt to rapid ventricular filling. There is often ascites and peripheral oedema, although signs of pulmonary congestion are absent.

Pericardial effusion

There may be a raised JVP with hypotension and quiet heart sounds.

Interpretation

Confirm the diagnosis

Tell the examiners that you would like to see an electrocardiogram (ECG) (saddle-shaped ST segments in pericarditis – often in only some leads reflecting patchy inflammation, small complexes in pericardial effusion), a chest X-ray (large globular heart shadow in pericardial effusion) and an echocardiogram. Acute pericarditis typically presents with pleuritic central chest pain, worse lying flat and relieved sitting forwards. Raising the legs of the supine patient to increase venous return classically induces sudden pericardial pain in pericarditis, which then eases as the legs are again lowered.

What to do next – consider causes

Tell the examiners that common causes of pericarditis include viruses (e.g. coxsackievirus), tuberculosis, autoimmune disease-associated serositis, malignancy, Dressler's syndrome (post myocardial infarction with fever), drugs, hypothyroidism and uraemia. Constrictive pericarditis is classically due to tuberculosis, but more usually due to viruses, and sometimes malignancy. All causes may lead to a pericardial effusion.

Consider severity / decompensation / complications

Pericarditis may lead to pericardial effusion and even tamponade (small-volume pulse, hypotension, raised JVP). An ECG might show small complexes. Echocardiography is essential to estimate the volume of fluid accumulated, assess cardiac contractility and guide diagnostic or therapeutic pericardiocentesis. Pericarditis may be part of a myopericarditis in which the troponin is elevated. Constrictive pericarditis causes diastolic dysfunction.

Consider function

Tell the examiners you would establish the limitations provoked by any symptoms.

Discussion

What ECG changes may be seen in pericarditis?

There is classically concave, saddle-shaped ST elevation, typically more widespread than in ST elevation myocardial infarction, involving more than one coronary territory. But it may be normal. T-wave inversion may occur before the ECG normalises. Atrial repolarisation is affected, leading to PR elevation in aVR (in association with ST depression) and PR depression elsewhere (in association with ST elevation). Q waves do not develop and reciprocal ST depression does not occur.

Table 3.25 Signs differentiating constrictive pericarditis from cardiac tamponade

Constrictive pericarditis	Tamponade
Prominent x and y descents	Prominent x descent
Kussmaul's sign positive	Kussmaul's sign negative
Pulsus paradoxus uncommon	Pulsus paradoxus present
Pericardial knock	No pericardial knock

How is pericarditis managed?

This is symptomatic with non-steroidal anti-inflammatory drugs. Anticoagulants should be discontinued and any underlying cause treated. Steroids may be given if it relapses.

Which signs help differentiate constrictive pericarditis from cardiac tamponade?

Differentiating signs are shown in Table 3.25.

How is constrictive pericarditis treated?

In addition to treating underlying causes, pericardectomy is the definite treatment to release constriction.

Nervous system

Examination of the nervous system

EXAMINATION OF THE NERVOUS SYSTEM – OVERVIEW

Context

Candidates (and examiners!) find neurological examination difficult. They find it difficult to know what to do, what they are looking for and how to interpret their findings.

The nervous system is complicated; the human brain comprises one hundred billion neurons, each neuron making thousands of synaptic connections with others, and it has been calculated that the number of possible permutations of brain activity or information exchange exceeds the number of elementary particles in the known universe. Not surprisingly, different neurologists and cognitive neuroscientists have different ways of approaching such a complex body system. And more than any other specialty, there is often a sense of inaccessibility to those outside it. Lists of signs are somewhere in memory, like fragments of jigsaw, but form no real picture. 'Absent ankle jerks and extensor plantars' is a list learned by rote, exonerated to a mythical proportion of difficulty.

Although science is poised to understand a lot more about the human brain, to demystify the walnut shaped piece of jelly that subserves all that humans think and do, neurologists and neuroscientists remain in the shallows. You may feel you have not set foot in the water, but remember that in this largely unexplored ocean your interpretations may be as valid as anyone's. To make some sense of the nervous system, it is necessary to oversimplify it, and there is nothing wrong with that. To get glimpses of how it really works, two things often help us. The first is to understand things from an evolutionary vantage; this often helps to explain why things might be so. The second is to understand neurological curiosities, anomalies and disease; these often help to explain how the normal brain works. More and more, study of curious diseases is providing insights into the murky neuroscientific ocean, exchanging it for a giant aquarium as the windows slowly slot into place.

Neurological examination is best performed in context. Rather than trying to examine everything hurriedly and with little grasp of what you are looking for, it is better to be selective. Patients with different neurological problems need different types of examination.

Levels of the nervous system

A basic grasp of how the different levels of the nervous system and patterns of signs that arise from disease at different levels helps candidates know what to do, what to look for and how to interpret their findings. Interpreting findings should be anatomical and pathological.

Anatomical interpretation of findings

Attempt to identify if there is one or more than one lesion and the level or levels involved (Box 3.17). Findings may form a recognisable syndrome such as Horner's syndrome or Parkinsonism, but diseases may also coexist. A combination of upper and lower motor neuron signs in an older patient is common with cervical myelopathy, multilevel radiculopathy and peripheral neuropathy. Remember that systems degenerate with age and as neuronal reserve declines so vision, hearing, balance, reflexes and gait can change. In general signs are more likely to represent pathology if there are associated symptoms. If you think 'perhaps the left triceps jerk is a little less brisk than the right', it may well be normal.

Pathological interpretation of findings

Consider which diseases are consistent with the anatomical findings. History taking is the most important part of neurological assessment because it helps localise the level and site of a lesion and determine its duration – intermittent unilateral headache for many years is likely to be migraine, abrupt hemiparesis and facial weakness cerebral ischaemia, worsening sensory symptoms over a few months in the median nerve distribution carpal tunnel syndrome and so forth. Since history taking is not possible in PACES, the examination schemes that follow are selective sequences appropriate for the cases that are likely to occur in PACES. With any examination, remember that neurology is a highly observational specialty. Much can be missed by stepping forward instantly to examine 'hands on'.

Box 3.17 **Levels of the nervous system**

- Cranial nerves (peripheral nerves of the head and neck)
- Cerebral hemispheres
- Brainstem
- Extrapyramidal system and cerebellum
- Spinal cord
- Nerve plexuses
- Nerve roots
- Specific nerves
- Neuromuscular junction
- Muscles

EXAMINATION OF THE CRANIAL NERVES

Introduction

Cranial nerves in context

When we examine the limbs we consider upper and lower neuron lesions. Cranial nerves are simply lower (motor, sensory or both) neurons. Examining them in order from I to XII detracts from the concept that these peripheral nerves connect proximally via their nuclei with central nerves and distally with neuromuscular junctions and muscles (Fig. 3.17). What we are really doing with so-called 'cranial nerve' examination is examining the head and neck and when examining head and neck neurology a functional approach is more logical than a numerical one – examining 'the eyes', 'visual fields', 'eye movements' and so on rather than 'the cranial nerves'.

The value of cranial nerve and long tract lesions in localisation

Cranial nerve nuclei are where cranial nerves synapse with their supranuclear pathways within the brainstem. Many brainstem lesions may, theoretically, be localised by cranial nerve lesions and long tract signs.

Cranial nerve lesions

Brainstem lesions can be localised in the vertical plane by cranial nerve lesions. The 12 nuclei broadly descend from

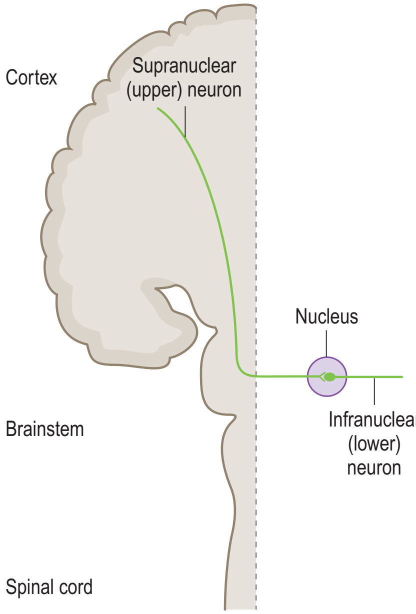


Figure 3.17 Supranuclear, nuclear and infranuclear arrangement of the nervous system.

midbrain to medulla (Fig. 3.18). In reality there are more than 12 nuclei, some nerves with a main nucleus and smaller satellite nuclei.

Long tracts

Brainstem lesions can be localised in the transverse plane by signs of damage to long motor and sensory tracts (motor being ventral to sensory).

Corticospinal tracts (Fig. 3.19) are long motor tracts that descend from the precentral gyrus of the frontal lobe, through the internal capsule, cerebral peduncle, midbrain and pons, and decussate at the medullary 'pyramids' to supply the contralateral limbs. They are sometimes called pyramidal tracts. Arm fibres lie medial to leg fibres. Fibres synapse at their destined ventral horn exit sites in the spinal cord. *Supranuclear pathways destined to innervate cranial nerves* descend with the corticospinal fibres as far as the brainstem where they decussate and synapse with and innervate their respective cranial nerve nuclei and cranial nerves, which may be pure motor, pure sensory, or both. Supranuclear fibres innervating the lower cranial nerves that mediate speech and swallowing are often called corticobulbar fibres (Fig. 3.19).

The *dorsal columns* carrying sensory information for accurate localisation of touch, vibration and proprioception synapse and decussate in the medulla and project to the contralateral thalamus and parietal lobe (Fig. 3.20). The *spinothalamic tracts* carrying pain and temperature information have already synapsed and crossed lower in the spinal cord and also project to thalamus and parietal lobe (Fig. 3.20). *Supranuclear fibres from sensory cranial nerves* and their nuclei (e.g. the trigeminal sensory nucleus) project to the contralateral thalamus and parietal lobe (Fig. 3.20). The exception is the corneal reflex, where evolution felt a rapid protective response would be best served by an involuntary relay between trigeminal nerve-mediated sensation and facial nerve-mediated eye closure within the brainstem. There is bilateral supranuclear innervation to the trigeminal motor nucleus, such that

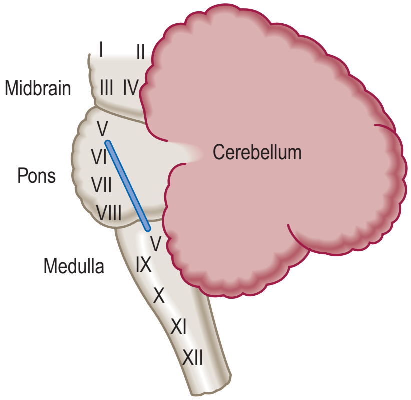

Midbrain
Pons
Medulla
I
II
III
IV
V
VI
VII
VIII
V
IX
X
XI
XII
Cerebellum

Figure 3.18 Location of cranial nerve nuclei in the brainstem; I–XII nuclei present bilaterally.

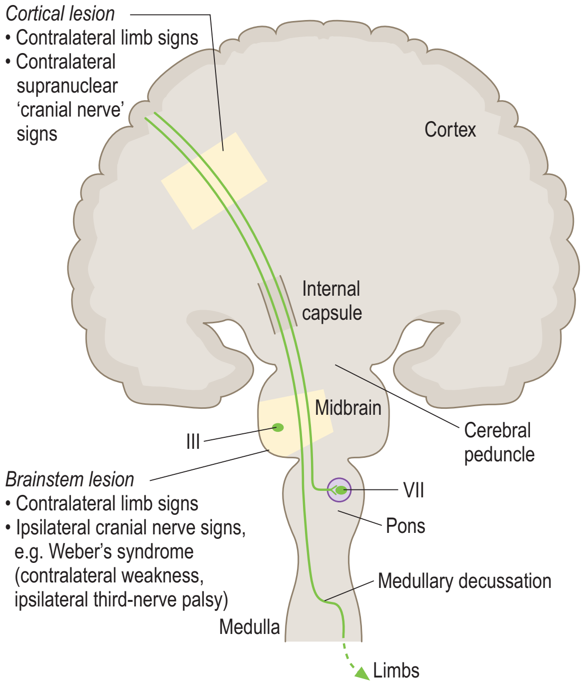

Cortical lesion
• Contralateral limb signs
• Contralateral supranuclear 'cranial nerve' signs
Cortex
Internal capsule
Midbrain
III
Cerebral peduncle
Brainstem lesion
• Contralateral limb signs
• Ipsilateral cranial nerve signs, e.g. Weber's syndrome (contralateral weakness, ipsilateral third-nerve palsy)
VII
Pons
Medullary decussation
Medulla
Limbs

Figure 3.19 Cortical versus brainstem lesions. Cerebellum not shown for simplification.

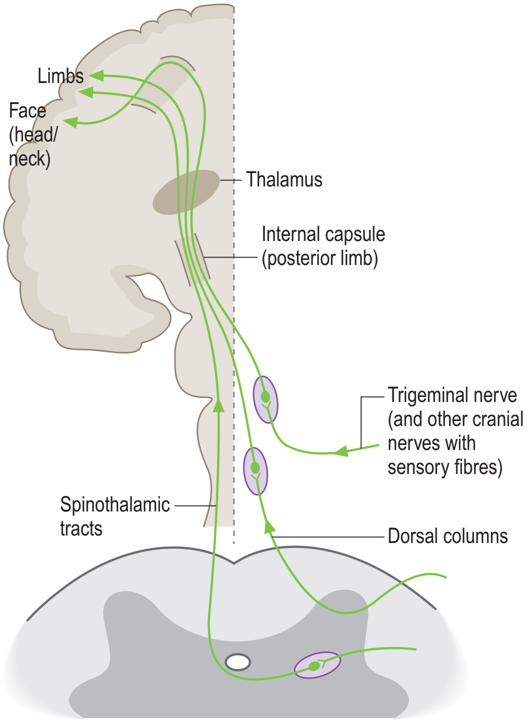

Limbs
Face (head/ neck)
Thalamus
Internal capsule (posterior limb)
Trigeminal nerve (and other cranial nerves with sensory fibres)
Spinothalamic tracts
Dorsal columns

Figure 3.20 Sensory pathways from the spinal cord to the parietal cortex via the brainstem.

chewing persists in the face of hemianaesthesia. Chewing is more important to survival than facial sensation!

All of this information has localising value (Box 3.18).

Implications of multiple cranial nerve lesions

Multiple cranial nerve lesions may occur where nerves run closely together (often resulting in the recognised syndromes in Box 3.19), in generalised disorders (e.g. myasthenia gravis) or as a result of multiple discrete lesions (e.g. basal meningitis, strokes).

Olfactory nerve (I)

Olfactory testing is seldom expected in PACES.

Box 3.18 **Brainstem versus cortical lesions and the value of cranial nerves in localisation**

Cortical lesions

A cortical lesion such as an internal capsule stroke may cause *contralateral long tract signs and contralateral supranuclear cranial signs* (Fig. 3.19). If the tongue and face are affected on the same side as a hemiparesis the lesion must be supranuclear to the twelfth and seventh nuclei, respectively. However, some cranial nerves, indeed most, receive bilateral supranuclear innervation and function is unaffected. The trigeminal motor nucleus is one example, and facial nerve fibres supplying the upper face another; 'spare parachutes' for chewing and eye protection carry survival advantages. Spare parachutes for the bulbar cranial nerves (IX, X, XII) often exist, but often require recruitment before they become affected – it is not uncommon following a cortical stroke to develop speech and swallowing problems that improve with rehabilitation as the brain's plasticity declares itself.

Brainstem lesions

A brainstem lesion may cause *contralateral long tract signs* (if the lesion is above the medullary decussation of the corticospinal tracts and dorsal columns; the spinothalamic tracts have already crossed in the spine and any pain and temperature loss is contralateral to the side of a brainstem lesion) with *ipsilateral cranial nerve signs* because the cranial nerve nuclei or nerves are damaged directly (Fig. 3.19). This combination is sometimes referred to as crossed signs. A lesion is, for example, at the level of the midbrain if III is involved, the pons if VI or VII is involved and the medulla if IX, XI or XII are involved. A brainstem lesion may extend bilaterally (e.g. demyelination, space-occupying lesion, basilar artery occlusion) causing bilateral motor or sensory long tract and cranial nerve signs.

Box 3.19 **Cranial nerve syndromes**

- Unilateral V, VII and VIII – cerebellopontine angle lesion
- Unilateral III, IV, V_1 and VI – cavernous sinus lesion
- Unilateral IX, X and XI – jugular foramen lesion
- IX, X, and XII – bulbar palsy

Eyes

Visual acuity (VA) – optic nerve (II)

VA testing is seldom expected in PACES. Problems with VA may arise from refractive errors, anterior eye disease such as cataracts or retinal disease.

- Ask the patient to close each eye in turn and read the letters on a near vision chart at 30 cm. Vision should be corrected with glasses if the patient wears them, but a pinhole could also be used to correct refractive errors as it filters out angled rays of light entering the eye. A 6 m Snellen wall chart is more accurate. Normal distance VA is 6/6, meaning that the eye sees at 6 m what it should see at 6 m. 6/60 (the letters on the 6/60 line are 10 times larger) means it sees at 6 m what it should see at 60 m. If letters cannot be seen, bedside tests such as counting fingers, seeing hands movements and perception of light may be performed.
- Test colour vision using a red hatpin. Central vision is colour (cones) and especially sensitive for red. Red desaturation, an impaired ability to detect red, suggests an optic nerve lesion.

Visual fields (VFs) – optic nerve (II)

Different patterns of VF abnormality arise from lesions at different sites (Case 3.16). VFs are divided vertically into nasal and temporal fields such that an object on your right looking ahead is in the temporal field of your right eye and the nasal field of your left eye. VF defects are described according to the patient's perspective and are homonymous if the same part of the VF is affected in each eye.

- Sit just under one arm's length away from the patient and at the same level. Cover one of their eyes, close your opposing eye and ask the patient to look at you. Slowly introduce a finger or white hatpin in a plane halfway between you and the patient from each quadrant (Fig. 3.21A), ensuring that the pin cannot be seen when you start. A white pin is used because peripheral vision is monochrome. Major VF defects can be screened for using the method shown in Figure 3.21B, asking the patient to tell you which index finger or hand is moving, right, left or both.
- Examine for a scotoma by moving the hatpin (a red one will detect more significant deficits) slowly at eye level in a temporal to nasal direction and asking the patient to tell you if it disappears or changes colour. In a central scotoma there will be loss of central vision. The blind spot 30° into the temporal field can be mapped in the same way. It corresponds to the optic disc.

Pupils – optic nerve (II), oculomotor nerve (III)

- Check pupils are of equal size and shape. Ptosis on the side of a larger pupil should alert you to a

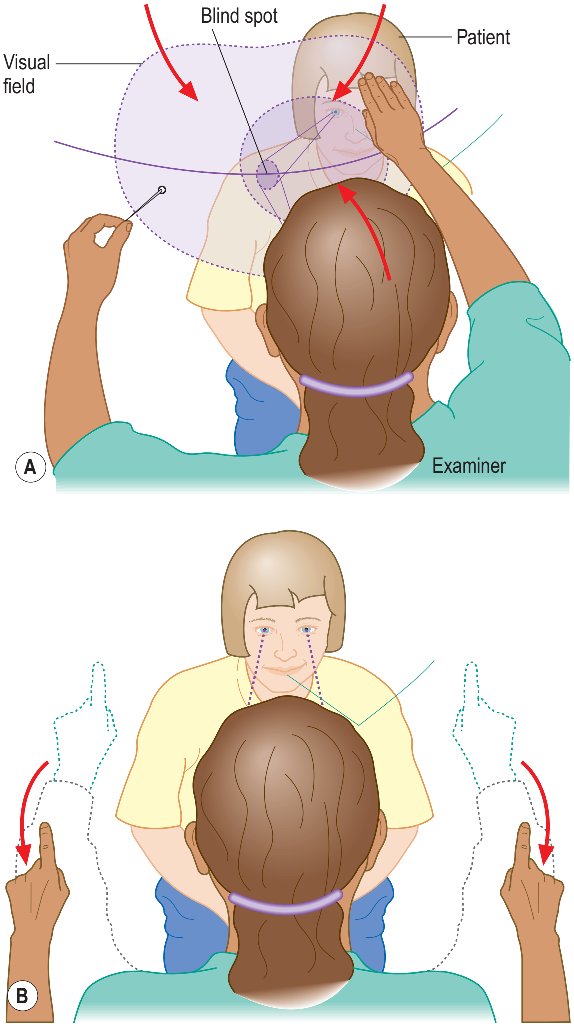

Visual field
Blind spot
Patient
A
Examiner
B

Figure 3.21 Visual field testing: (A) confrontation method, (B) screening for large defects.

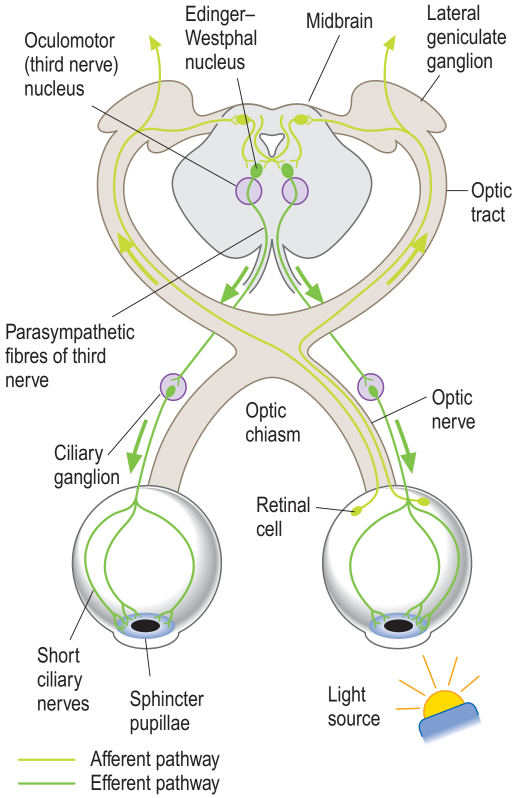

Oculomotor (third nerve) nucleus
Edinger–Westphal nucleus
Midbrain
Lateral geniculate ganglion
Optic tract
Parasympathetic fibres of third nerve
Optic chiasm
Optic nerve
Ciliary ganglion
Retinal cell
Short ciliary nerves
Sphincter pupillae
Light source
Afferent pathway
Efferent pathway

Figure 3.22 The light reflex.

third-nerve palsy, and on the side of a smaller pupil to Horner's syndrome.

- Place your finger 10 centimetres in front of the patient's nose and check the accommodation response (Box 3.20). The eyes should constrict as they converge.
- Check the direct and consensual light reflexes by shining the light twice in each eye (Fig. 3.22, Box 3.20).
- Note any afferent pupillary defect by swinging the light repeatedly (the swinging light test) from eye to eye, dwelling for a second or two on each eye (Box 3.21). Observe paradoxical dilatation of the pupil of an affected eye, implying a damaged afferent pathway (optic nerve).

Box 3.20 **The light and accommodation reflexes**

Light reflex

Light impulses travel along the optic nerve and both optic tracts. Approximately 10% of fibres reaching the level of the lateral geniculate ganglion subserve the light reflex and connect with both Edinger–Westphal nuclei (and adjacent third-nerve nuclei) in the periaqueductal matter of the midbrain. Parasympathetic fibres, entwined around both oculomotor nerves, are 'excited' by the light impulses, and stimulate the ciliary ganglion, ciliary nerves and ultimately the pupillary sphincter muscle of each pupil causing bilateral pupillary constriction.

Accommodation reflex

A similar efferent mechanism subserves accommodation, although the afferent pathway is in the frontal lobe rather than the optic nerve. The third-nerve nuclei also control the action of the medial rectus muscles and convergence. The ciliary nerves also supply the ciliary muscle, altering the lens's shape for focusing. Many more ciliary fibres are dedicated to the ciliary muscle than to the pupillary muscle and the accommodation reflex is often regarded as 'stronger' than the light reflex. This may be the reason why accommodation is preserved in otherwise unreactive Argyll Robertson pupils.

Box 3.21 How the swinging light test detects an afferent pupillary defect (APD)

This relies on the fact that the pupils receive dual innervation from the midbrain.

A Shining light into the affected eye causes absent or sluggish direct and consensual responses.

B Shining light into the normal eye stimulates normal direct and consensual responses.

C If there is complete damage to the afferent pathway of the affected eye, whatever lighting the normal eye (dominant response) is exposed to will determine the size of both pupils. When light is swung back into the affected eye the normal pupil dilates and so does the affected pupil. If there is partial damage to the afferent pathway recovery from B (the dominant response) is swifter and stronger than the sluggish response to A, so the affected eye still dilates. The latter is known as a relative afferent pupillary defect. An APD is also known as a Marcus Gunn pupil.

Eye movements – oculomotor nerve (III), trochlear nerve (IV), abducens nerve (VI)

- Observe the eyes in primary gaze. Misalignment may be due to a latent strabismus (constant convergent or divergent strabismus in all directions of gaze), a third-nerve palsy or skew deviation in which the eyes are aligned in different vertical planes (brainstem pathology).
- Observe slow, smooth pursuit movements used for fixation on a moving object (the lioness on the Serengeti eyeing a roaming zebra or gazelle). Do this by gently fixing the patient's head with one hand and ask the patient to follow the index finger of your other hand using midline horizontal and vertical movements, not a letter H. Look for an ocular palsy due to a lesion of III, IV or VI. Be alert to more than one lesion. Ask about double vision. Also be alert to supranuclear disorders of eye movements that may not result in double vision such as a lateral-gaze palsy (frontal or parietal lesion when the patient looks away from the side of the lesion or pontine lesion when the patient cannot look away from the side of the lesion) or a vertical-gaze palsy (upper brainstem lesion).
- Observe faster saccadic movements, the rapid movement from one point of fixation to another (the zebra or gazelle catches sight of the lioness), asking the patient to look from side to side. This may elicit internuclear ophthalmoplegia.
- Note any nystagmus, normal at extremes of gaze.
- Note any ptosis.

Fundoscopy

Fundoscopy is discussed in Station 5.

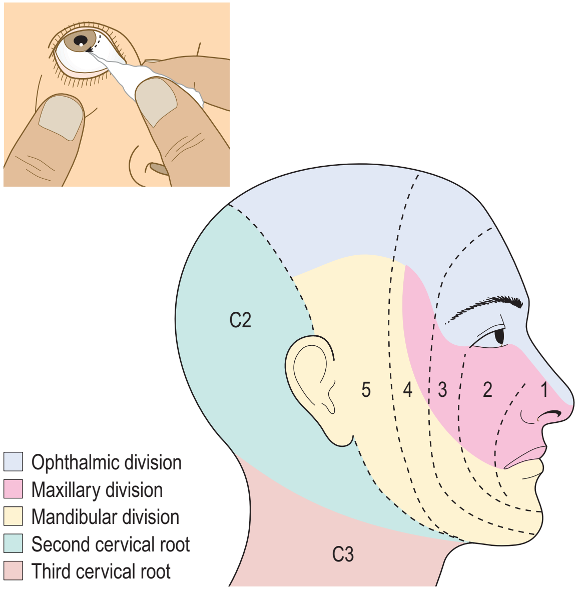


Figure 3.23 Facial sensation. Insert: Testing the corneal reflex. Areas 1–5 indicate the distribution of sensory fibres from the fifth nerve's long nucleus that extends from the pons (1) to the upper cervical cord (5); the implication of this is that fifth-nucleus lesions, unlike fifth-nerve lesions, produce (bilateral if both nuclei affected) 'onion skin' patterns of facial sensory loss.

Trigeminal nerve (V)

The trigeminal nerve is sensory to the face and motor for the muscles of mastication.

- Feel for any wasting of the masseters, the muscles of jaw closure.
- Ask the patient to clench their teeth (masseters) and open their mouth against the resistance of your hand on their chin (pterygoids).
- Test light touch and pinprick in the ophthalmic (V$_1$), maxillary (V$_2$) and mandibular (V$_3$) distributions (Fig. 3.23).
- Tell the examiners that you would check the corneal reflex (Fig. 3.24) with a wisp of cotton wool (touching the cornea, not the white sclera), its absence often the first sign of a trigeminal lesion.
- Test the jaw jerk (Fig. 3.25), which can be brisk with bilateral supranuclear lesions above the level of the pons (e.g. pseudobulbar palsy).

Facial nerve (VII)

This is motor to the face and provides taste to the anterior two-thirds of the tongue.

- Look at facial symmetry, noting the nasolabial folds and forehead wrinkles and watch spontaneous movements such as smiling and blinking.
- Ask the patient to show you their teeth, whistle or blow out their cheeks, close their eyes tightly and

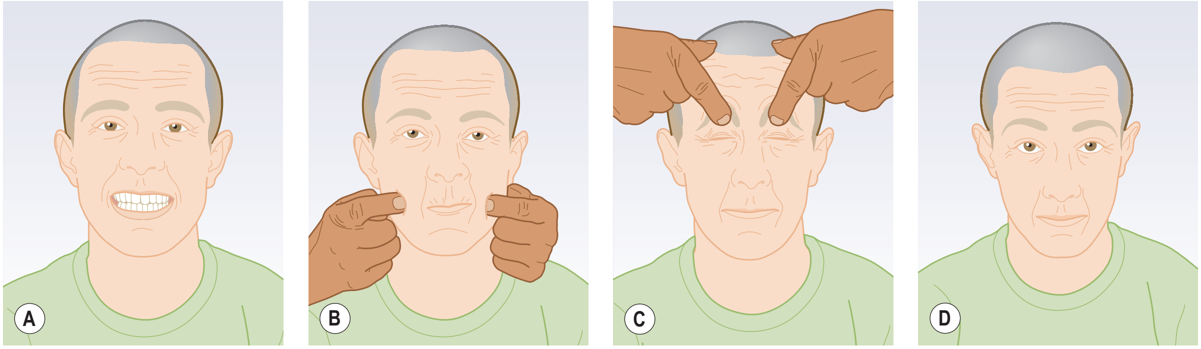


Figure 3.24 Facial nerve examination. Ask the patient to do the following: (A) show me your teeth, (B) puff your cheeks out, (C) close your eyes tightly and do not let me open them, and (D) raise your eyebrows.

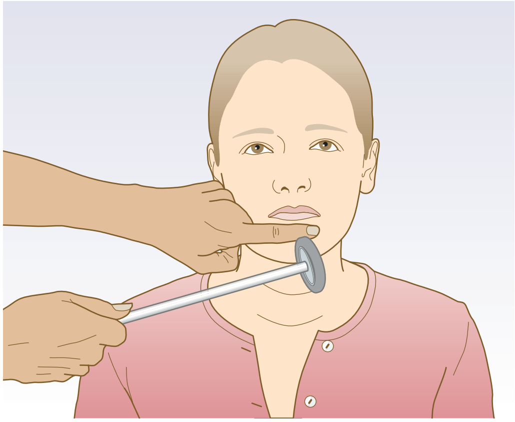


Figure 3.25 Eliciting the jaw jerk.

look up at the ceiling, again looking for symmetrical movement (Fig. 3.24). Bell's phenomenon (eye turns upwards on attempted closure) is due to a lower motor neuron lesion.

- Compare power in the forehead and lower face. Since upper facial muscles receive bilateral supranuclear innervation, unilateral upper motor neuron lesions spare the forehead whereas a facial nerve palsy (lower motor neuron) paralyses the upper and lower face (Case 3.25). Bilateral facial nerve lesions sometimes occur.

Ptosis is not due to a facial nerve lesion.

Hearing

Hearing testing is seldom expected in PACES. Clinical tests can be unreliable, as demonstrated by formal audiometry.

Rinne's test

Rinne's test (Fig. 3.26A) compares sound from a vibrating 512 Hz tuning fork on the mastoid (bone conduction) with the external auditory canal (air conduction). Normally air conduction is better than bone conduction (bone, denser than air, is actually a better conductor of sound but here 'conduction' misleadingly refers to the unimpeded transmission of sound through the air and external canal to the middle ear and inner ear), by convention a Rinne-positive test. If bone conduction is better, this implies conductive deafness (everything other than the sensorineural aspect of hearing is conductive), usually due to middle ear disease or wax.

Weber's test

In Weber's test (Fig. 3.26C), sound should be heard in both ears equally when the tuning fork is applied to the central forehead or vertex. In sensorineural deafness, sound is not detected by the affected ear. In conductive deafness sound is louder in the affected ear although this phenomenon is difficult to explain. Certainly, when a tuning fork is placed directly on bone, there is no significant sound transmission through the air and all conduction is through bone to the inner ear. Any additional solid material in the ear (e.g. wax, tympanosclerosis, middle ear debris or even poking a finger into the ear!) is likely to attenuate the normal energy loss at a bone–air interface and enhances sound transmission to the inner ear from the vertex.

Bulbar function – speech and swallowing

The lower ('bulbar') cranial nerves IX, X and XII are integral to speech and swallowing. The proximity of these nerves implies that several combinations of lesion are possible, and that presenting symptoms may be similar whatever the diagnosis – loss of strength in speech and swallowing with hoarseness, nasal speech, nasal regurgitation of fluids or food particles with aspiration and attacks of choking – in other words, a bulbar palsy (Case 3.26).

Glossopharyngeal nerve (IX)

This is mostly sensory, relaying information from the palate, pharynx and posterior third of the tongue via the

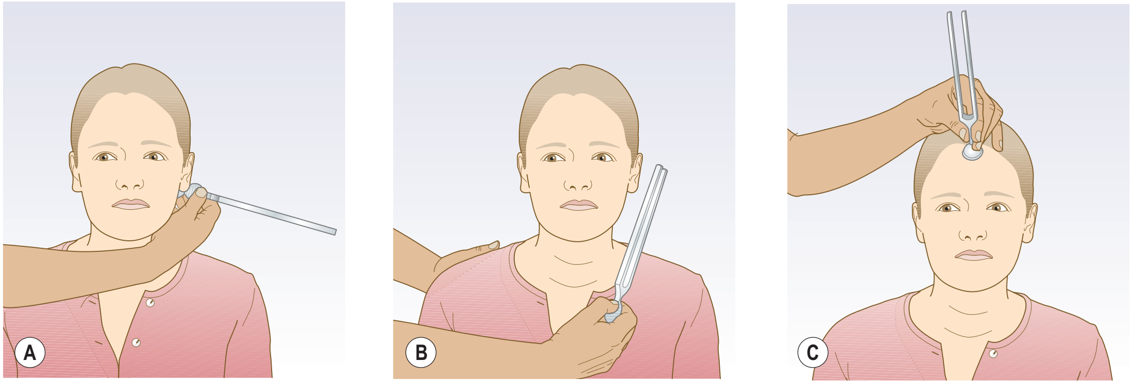


Figure 3.26 Rinne's test. Bone conduction (A) and air conduction (B). (C) Weber's test; placing the tuning fork on the teeth is more sensitive but only to be done with care.

trigeminal nucleus to the sensory cortex. It is motor only to stylopharyngeus. A glossopharyngeal lesion is rare in isolation and invariably part of a wider bulbar palsy.

- Touch the palate each side with an orange stick or touch the pharyngeal wall each side with the patient saying 'Aah', asking the patient to compare right and left.
- Touching the posterior third of the tongue is of less value.
- The gag reflex (sensory via IX, motor to palate via X) is usually too gross to test and unreliable, not present in many people.

Vagus nerve (X)

This is motor to the palate, pharynx, larynx and vocal cords and sensory to the tympanic membrane, external auditory meatus and external ear.

- Watch the patient say 'Aah'. The palate and uvula normally move upwards. In a vagus lesion the paralysed side is immobile and tends to be pulled towards the intact side. The palate fails to elevate and the uvula is seen dragged across to the unaffected side. It may be completely immobile in bilateral vagus lesions. These problems lead to the bulbar palsy symptoms described above.
- Assessment should include voice and cough as well as palatal movements. A paralysed vocal cord lies limply abducted to the midline, giving rise to a hoarse voice and a bovine cough.

Since sensory fibres from X are conveyed in the auricular branch, malignant lesions of the throat may sometimes cause earache, as may the common cold.

Hypoglossal nerve (XII)

This is motor to the tongue.

- Observe the tongue at rest. It is paralysed on the side of a lesion and deviates to the side of that lesion. It may also be unilaterally wasted.
- On attempted tongue protrusion, the deviation can become more obvious.
- Tongue fasciculation is best observed with the tongue at rest inside the mouth as normal rippling movements can occur when the tongue exerts itself.

Coordination of cranial nerves in swallowing

Perhaps the best test of overall bulbar function is to ask the patient to drink a glass of water. Swallowing is a complex process involving many cranial nerves and comprises a voluntary phase, a reflex phase and an oesophageal phase. In the voluntary phase VII holds the mouth shut, IX relays information about food bolus position to the sensory cortex, V controls chewing, IX senses the arrival of the bolus at the palate and XII pushes the chewed bolus up and back against the palate. In the reflex phase XII pulls the hyoid upwards and forwards to bring the larynx beneath the back of the tongue, IX, via stylopharyngeus, assists the hyoid elevators and lifts the larynx forwards and X elevates the palate to occlude the nasopharynx (preventing nasal regurgitation), flips the epiglottis forwards over the top of the elevated and tilted larynx (preventing food falling into trachea), dilates the hypopharynx (allowing the bolus to fall into the oesophagus) and initiates oesophageal peristalsis.

Accessory nerve (XI)

This innervates the trapezius and sternocleidomastoid muscles.

- Test trapezius by asking the patient to shrug their shoulders against resistance (Fig. 3.27A).
- Test the sternocleidomastoids by asking the patient to turn their head against resistance (Fig. 3.27B). The right sternocleidomastoid turns the head to the left and vice versa.

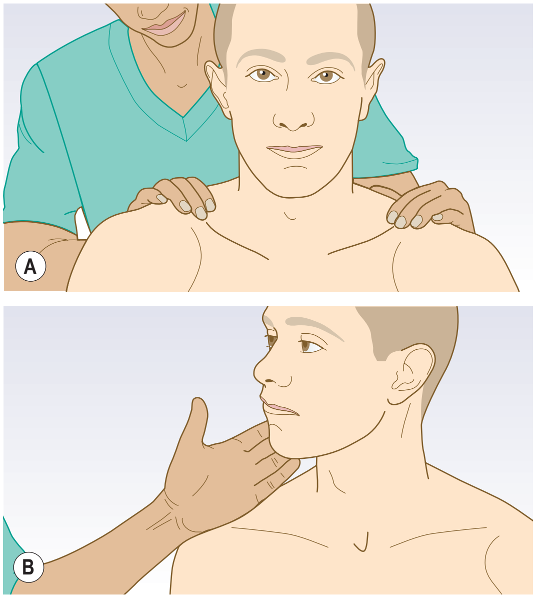


Figure 3.27 Testing the accessory nerve: (A) trapezius, (B) left sternocleidomastoid.

Summary

A summary of the cranial nerve examination sequence is in the Summary box.

SUMMARY BOX – CRANIAL NERVE EXAMINATION SEQUENCE

- Test visual acuity and then colour vision using a red hatpin.
- Test visual fields (an initial screen detects major homonymous defects).
- Check pupil size and shape.
- Test the accommodation reflex.
- Test the direct and consensual light reflexes and check for an afferent pupillary defect.
- Look at the eyes in primary gaze and then test eye movements.
- Note any internuclear ophthalmoplegia.
- Note any nystagmus.
- Note any ptosis.
- Test masseter strength.
- Test touch in all the divisions of the trigeminal nerve and tell the examiners you would check for a corneal reflex.
- Look at facial symmetry and test facial movements, noting any upper and lower facial discrepancy.
- Tell the examiners you would formally assess hearing in the presence of symptoms or in the presence of cerebellopontine neuropathies.
- Test palatal sensation.
- Test uvula and palatal movement.
- Look at the tongue at rest inside the mouth for deviation, wasting and fasciculation and then look for more obvious deviation of a protruded tongue.
- Test the accessory nerve.

EXAMINATION OF HIGHER CORTICAL FUNCTION AND SPECIFIC LOBES

Higher cortical function

Examining higher cortical function adequately is complex and cannot be performed in PACES. A 30-point mini-mental state examination is frequently performed on the wards, and a 10-point or 4-point abbreviated mental test score an initial clerking screen (Fig. 3.28).

Lobe syndromes

The cranial nerves send sensory information to the brain and receive motor information from it. Likewise, the rest of the body, through peripheral nerves and nerve roots, sends sensory information to the central nervous system and receives motor information from it. Some of this information does not involve the hemispheres of the cerebral cortex – the corneal reflex, for example, and spinal reflexes. But for most information, the cortex is involved, perceiving everything in our world and initiating almost everything we do. Its different lobes (Fig. 3.29) have specific functions.

The frontal lobe

This is a motor lobe. It plans, initiates and 'executes' tasks, known as executive function. The precentral gyrus puts thoughts into action; it is here that the cascade of messages to move a body part begins. Functions of the frontal lobe are shown in Box 3.22. The posterior parts of the lobe are most important to motor function, the more anterior parts to behaviour. Frontal lobe disease may result in those features in Box 3.23. The frontal lobes not only inhibit undesirable behaviour but also primitive reflexes that are present at birth. These may be disinhibited by frontal lobe disease.

Connections between different parts of the brain explain many neurological signs. Patients with Parkinsonism may have a positive glabellar tap because of disease involving the frontal lobe's extrapyramidal connections.

Box 3.22 **Functions of the frontal lobe**

- Planning, organising, sequencing, abstracting, initiation, judgement, self-evaluation and insight
- Initiation of movement
- Speech expression involving Broca's speech area (in the dominant hemisphere)
- Voluntary control of micturition
- The more enigmatic aspects of thinking and behaviour such as wisdom, intelligence, ambition, moral sense and judgement, in combination with all parts of the cortex in ways in which science has limited understanding
- Acquired social behaviour

Mini-mental state examination (MMSE)

ONE POINT FOR EACH ANSWER

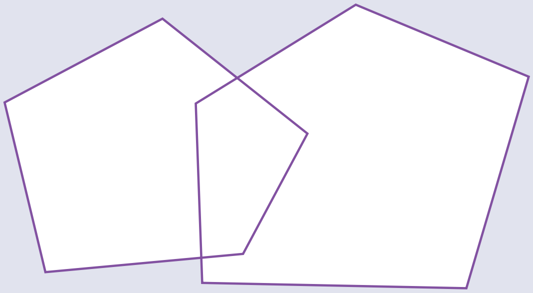
ORIENTATION	Year Month Day Date Time	____/5
	Country Town District Hospital Ward	____/5
REGISTRATION	Examiner names 3 objects (e.g. apple, table, penny) Patient asked to repeat (1 point for each correct) then patient to learn the 3 names repeating until correct	____/3
ATTENTION AND CALCULATION	Subtract 7 from 100, then repeat from result Continue 5 times: 100 93 86 79 65 Alternative: spell 'WORLD' backwards – dlrow	____/5
RECALL	Ask for names of 3 objects learned earlier	____/3
LANGUAGE	Name a pencil and watch	____/2
	Repeat 'No ifs, ands or buts'	____/1
	Give a 3-stage command. Score 1 for each stage, e.g. 'Place index finger of right hand on your nose and then on your left ear'	____/3
	Ask patient to read and obey a written command on a piece of paper stating 'Close your eyes'	____/1
	Ask patient to write a sentence. Score if it is sensible and has a subject and a verb	____/1
COPYING	Ask the patient to copy a pair of intersecting pentagons: 	____/1
	TOTAL	____/30

Figure 3.28 Mini-mental state examination.

The parietal lobe

The parietal lobe contains the sensory cortex or post-central gyrus. Unlike the frontal lobe, the parietal lobe very much senses, and is concerned with appreciating, the world around us, creating a three-dimensional representation of the spatial layout of the external world, and also of your body in that three-dimensional representation. Both the dominant and non-dominant parietal lobes are concerned with recognition and awareness. Both relay the parietal radiations of the visual pathways. Disease in a parietal lobe may manifest itself broadly in one of two ways (Box 3.24).

Lesions may cause a single problem or a recognised syndrome (Case 3.30 Agnosias and apraxias). The dominant parietal lobe is usually left sided (even in left-handed

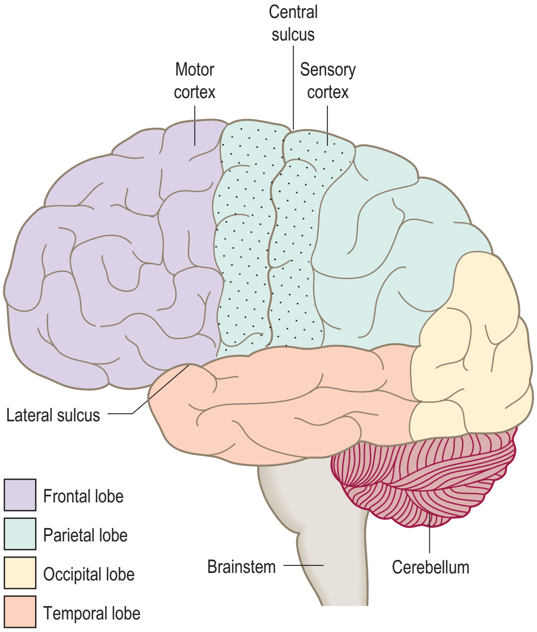


Figure 3.29 Lobes of the brain.

people, whose 'dominant' hemisphere we often assume as being the right). There is much overlap of dominant and non-dominant parietal lobe function, but apraxias are common after left parietal damage and neglect or sensory/visual inattention after right parietal damage.

The temporal lobe

The temporal lobe subserves memory (hippocampus and other areas) and emotion, certain aspects of perception, interpretation of numbering and colour, central representation of hearing, taste and smell, speech interpretation, transmission of visual impulses via the temporal visual radiations, and some aspect of behaviour via frontal lobe connections. Lesions may result in memory impairment, auditory agnosia (temporo-parietal connections), cortical deafness (if bilateral) and receptive dysphasia.

Box 3.23 **Potential effects of frontal lobe disease**

- Executive dysfunction and apathy (loss of initiative) and abulia (loss of spontaneity)
- Akinesia (difficulty with movement)
- Motor or expressive dysphasia (if dominant hemisphere)
- Incontinence
- Behavioural and mood disturbance and disinhibition

Primitive reflexes

- Grasp – stroking the palm induces a grasp
- Palmomental – firmly stroking the thenar eminence induces an ipsilateral grimace
- Rooting – stroking the cheek induces a gnawing mouth movement
- Sucking – touching the lips promotes sucking
- Snout – tapping the upper lip makes it pucker upwards
- Glabellar – tapping the forehead stimulates eye closure

Box 3.24 **Two important manifestations of parietal lobe disease**

Agnosias

There is *difficulty in recognising things*, despite intact sensory pathways peripheral to the parietal lobe. These problems with recognition are often termed agnosias.

Apraxias

There is *difficulty in performing tasks*, not because of any problem with motor nerves or muscles, which are all intact, but because the parietal lobe fails to process information about the environment. It would normally pass on this processed information to the frontal lobe, which in turn would normally initiate a course of action in response to it. These problems with performing tasks are often termed dyspraxias or apraxias.

The limbic system

The cerebral hemispheres perceive and initiate. They contact the outside world through sensory and motor pathways. But what of the inside world? There is extreme complexity in the visual pathways relaying what we see, but we always see a particular object in the same way. A monkey always looks like a monkey, a giraffe a giraffe, and we would not mistake one for another. But the visual pathways are crude compared with mechanisms of recognition, learning, thought and emotion. The limbic system is a deep part of the brain, part of the medial temporal lobes, where science has more questions than answers. It has to do with memory. It is also thought to be a centre for smell. Have you noticed that some smells instantly evoke distant memories?

The occipital lobe

The occipital lobe is the common endpoint of the visual nerve pathways. Lesions may result in cortical blindness, visual agnosia (parieto-occipital connections) or specific visual processing defects such as impaired perception of colour or movement.

EXAMINATION OF SPEECH AND LANGUAGE

Ensure that the patient can hear, then consider in turn if there is:

- Dysphasia
- Dysarthria
- Dysphonia.

Dysphasia

Types of dysphasia

Dysphasia is a disorder of language and refers to the inability to understand or find words (Table 3.26) because of a lesion in the dominant (usually left) hemisphere. As well as *difficulty understanding or finding words* from the brain's lexicon, common after strokes and causing frustration to patients, dysphasia can be *semantic or fluent* (speech fluent but irrelevant or nonsensical, usually with loss of insight, common in frontotemporal dementia) or *phonetic*, in which a word is almost correct (e.g. bat instead of ball).

Wernicke's area recognises sounds as language, but a higher concept area is required to convert sounds into meaning. This concept area then connects to Broca's area, where speech output is generated. A direct connection, the arcuate fasciculus, also exists between Wernicke's and Broca's areas. Transcortical sensory dysphasia is similar to receptive dysphasia but with preserved repetition and is caused by a lesion in the parietal–occipital concept area. Transcortical motor dysphasia is similar to expressive dysphasia but with preserved repetition and is the result of an incomplete lesion in Broca's area. Conductive dysphasia refers to preserved comprehension and output with loss of repetition and is the result of a lesion in the arcuate fasciculus. Difficulty naming objects, or nominal dysphasia, is the result of an angular gyrus lesion.

Examining for dysphasia

- Introduce yourself and ask a few simple questions, e.g. 'Can you tell me your name and date of birth?'
- Is there receptive dysphasia? Give a simple command, e.g. 'Close your eyes/With your right hand touch your nose' and then more complex, two-step or three-step commands.
- Is there expressive dysphasia? Get the patient talking further, e.g. 'Tell me a little about where you live.'
- Is there global dysphasia? If the patient cannot perform either task, there is global dysphasia (the lesion affects both receptive and expressive areas).
- Is there nominal dysphasia? Ask the patient to name some objects, e.g. 'What is this?' (show pen, tie and watch). If unable to name objects, ask 'Is it a ... ?'
- Assess word-finding ability, e.g. 'Name as many animals as you can think of.'
- Assess repetition by asking the patient to repeat a sentence, e.g. 'A giraffe is a tall, graceful animal.'
- Tell the examiners that you would assess reading and writing; similar categories of problem can occur with other aspects of language such as reading and writing (dyslexia and dysgraphia).

Dysarthria

Types of dysarthria

Dysarthria refers to impaired articulation and is the result of a lesion in any of the structures coordinating voice production:

- Upper motor neuron lesion (pseudobulbar palsy)
- Extrapyramidal lesion, e.g. Parkinson's disease
- Cerebellar lesion
- Lower motor/cranial nerve lesion (bulbar palsy)
- Neuromuscular junction lesion (myasthenia)
- Myopathy
- Local lesion of the palate, tongue or lips.

Examining for dysarthria

- Ask the patient to say some simple and more difficult (eleven benevolent elephants, baby hippopotamus) phrases.
- The sequence ppp, lll, kkk and a cough is a rapid screen for lip, tongue, palate and vocal cord function.

Figure 3.30 can be used to determine the type of dysarthria; Box 3.25 describes how to differentiate bulbar from pseudobulbar palsy.

Dysphonia

Types of dysphonia

Dysphonia refers to impaired voice production or phonation due to a lesion in the vocal cords or larynx (such as laryngitis) or vagal nerve supply. It is common when muscles are weak, as in Parkinson's disease.

Table 3.26 Receptive and expressive dysphasia

	Receptive dysphasia	Expressive dysphasia
Problem	Inability to understand	Inability to express, despite comprehension
Clinical findings	May be fluent, but words meaningless	Can cause immense frustration to patients, who know in their minds what they want to say but cannot get the words out (if less severe can answer questions and speak spontaneously but often struggle, making mistakes)
Location of lesion	Wernicke's area in the temporal lobe (may be a visual field defect)	Broca's area in the frontal lobe (connected to Wernicke's area by the arcuate fasciculus)

In reality it is less useful to distinguish expressive and receptive dysphasia, and the concept of two discrete language areas is somewhat artificial. Dysphasia usually involves both expressive and receptive components, and testing more complex sequence tasks or non-verbal language skills in a patient with obvious word-finding difficulty who appears to understand simple commands can reveal this to be so.

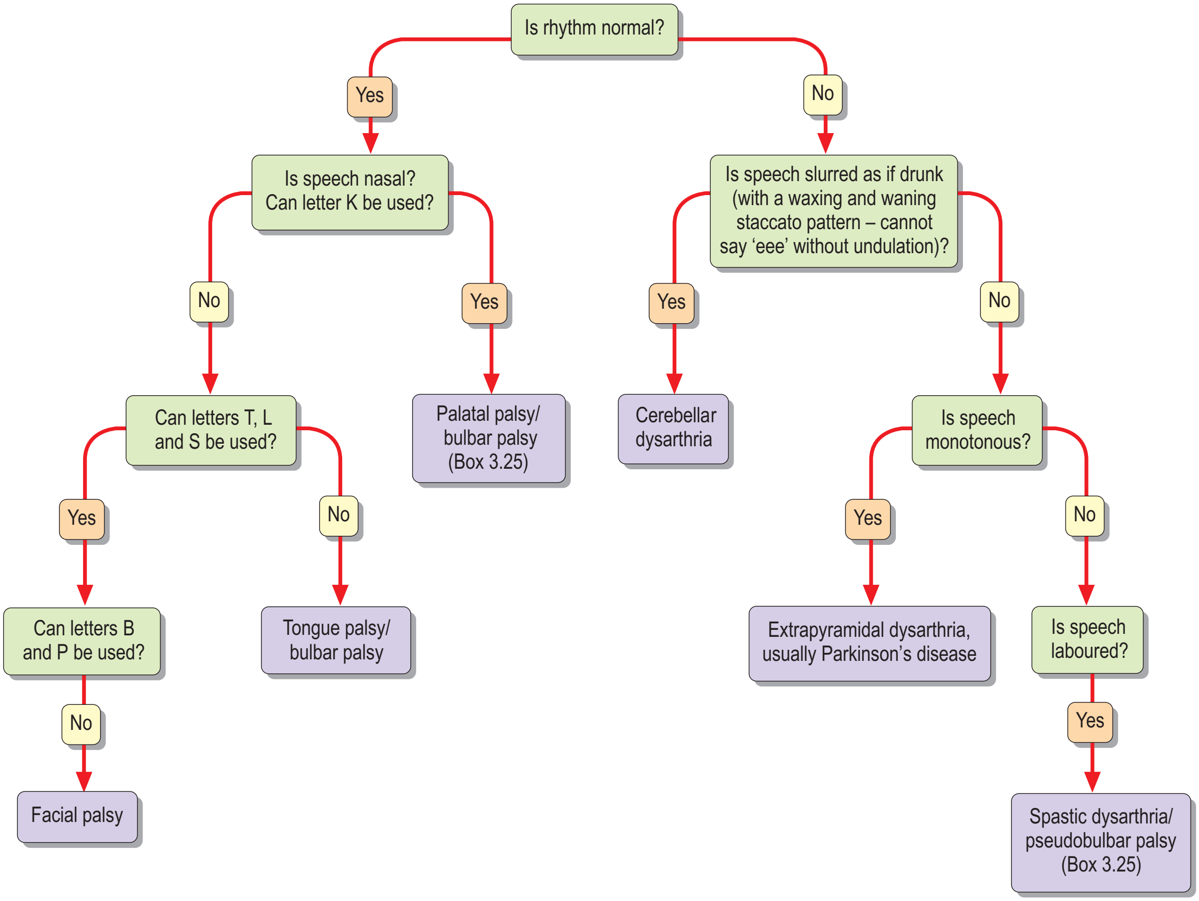

Is rhythm normal?
Yes
No
Is speech nasal? Can letter K be used?
No
Yes
Can letters T, L and S be used?
Yes
No
Can letters B and P be used?
No
Facial palsy
Tongue palsy/ bulbar palsy
Palatal palsy/ bulbar palsy (Box 3.25)
Is speech slurred as if drunk (with a waxing and waning staccato pattern – cannot say 'eee' without undulation)?
Yes
Cerebellar dysarthria
No
Is speech monotonous?
Yes
Extrapyramidal dysarthria, usually Parkinson's disease
No
Is speech laboured?
Yes
Spastic dysarthria/ pseudobulbar palsy (Box 3.25)

Figure 3.30 Dysarthria.

Box 3.25 **Bulbar and pseudobulbar palsy**

Bulbar palsy

Bulbar palsy refers to infranuclear or lower motor neurone disease, usually involving cranial nerves X (palate) or XII (tongue) with flaccid, nasal speech. Nasal speech / escape is the characteristic sign of bulbar palsy and nasal regurgitation of fluids and food with choking or aspiration may be prominent. Analogies are 'drowning' or 'choking' and a sense that 'everything is in the way'. The tongue seems too big for the mouth and seems to hang out with salivary pooling. It is a bit like replacing a human's tongue with a Labrador dog's tongue! Patients sometimes say it feels as if the mouth is numb like being at the dentist and cannot spit out toothpaste.

Pseudobulbar palsy

Pseudobulbar palsy refers to supranuclear or upper motor neurone disease with spastic speech. The tongue appears small and 'tight', and cannot be protruded, lying immobile on the floor of the mouth. Analogies include 'high-pitched', 'Donald Duck', 'hot potato' or 'strained' speech. Bilateral supranuclear innervation of the lower (bulbar) cranial nerves necessary for speech and swallowing means that bilateral cortical or brainstem lesions are required to induce a pseudobulbar palsy. Causes include bilateral internal capsule strokes or demyelination. Dysarthria and swallowing problems in a cortical stroke are due to unilateral supranuclear disease, often a combination of facial and bulbar weakness, but the spare parachute afforded by bilateral innervation to the swallowing muscles means that it is a much-attenuated form of pseudobulbar palsy.

Examining for dysphonia

- Determine whether the patient coughs or produces a sustained 'eee'. Dysphonia with a normal cough suggests a local (laryngeal) lesion. A bovine cough (without an explosive start) suggests vocal cord palsy.

Summary

A summary of the speech and language examination sequence is given in the Summary box.

SUMMARY BOX – SPEECH AND LANGUAGE EXAMINATION SEQUENCE

- ◆ Introduce yourself and ask a few simple questions, e.g. 'Can you tell me your name and date of birth?'
- ◆ Test for receptive dysphasia with a simple command, e.g. 'Close your eyes/With your right hand touch your nose' and then more complex, two- or three-step commands.
- ◆ Test for expressive dysphasia by getting the patient to talk more, e.g. 'Can you tell me a little about where you live?'
- ◆ Consider global dysphasia.
- ◆ Test for nominal dysphasia by asking the patient to name some objects. If unable to name, ask 'Is it a …?'
- ◆ Assess word-finding ability, e.g. 'Name as many animals as you can think of.'
- ◆ Assess repetition by asking the patient to repeat a sentence, e.g. 'A giraffe is a tall, graceful animal.'
- ◆ Tell the examiners that you would assess reading and writing.
- ◆ Use the sequence 'ppp, lll, kkk' and a cough as a rapid screen for lip, tongue, palate and vocal cord function.
- ◆ Ask the patient to say some phrases, e.g. 'eleven benevolent elephants, baby hippopotamus'.

EXAMINATION OF COORDINATION

The motor cortex exerts voluntary or conscious control of movement via its descending motor pathways to cranial nerves and corticospinal tracts and conscious sensory information travels via the ascending dorsal columns, spinothalamic tracts and sensory pathways from cranial nerves to the thalamus and sensory cortex.

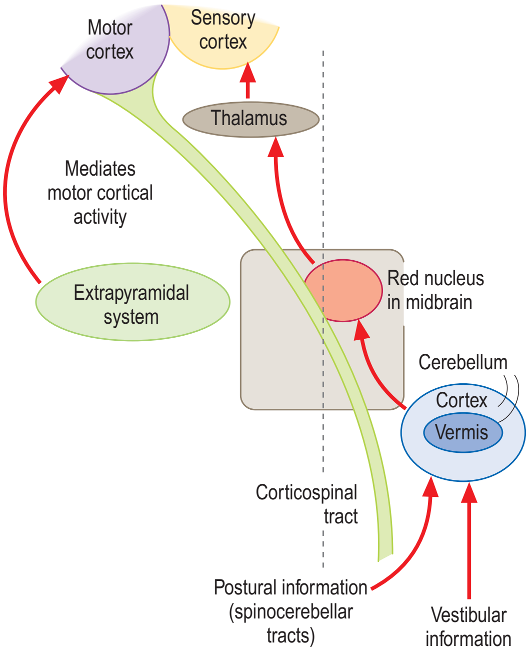
That conscious motor pathways are not enough to control movement is evident from diseases of the extrapyramidal system. The extrapyramidal system adds unconscious fine-tuning to every move we make.

That conscious sensory pathways are not enough to appreciate the body's position in space is evident by diseases of the cerebellum. The cerebellum sends unconscious feedback to the cortex about every move we make.

There is, in essence, a loop (Fig. 3.31). The motor cortex initiates activity, movements are adjusted by the extrapyramidal system, and the cerebellum provides feedback information about the movements made.

When examining coordination, be aware that the dominant side may have a slight advantage.

- Look for nystagmus.
- Ask the patient to hold their arms outstretched and close their eyes. Look for any oscillation.



Note that a left cerebellar lesion will cause a *left*-sided movement disturbance and vice versa

Figure 3.31 The loop.

- Ask the patient to touch your finger, held out about an arm's length away. Look for an intention tremor or overshoot (past pointing). Then ask the patient to touch their nose. Repeat this movement at faster speeds, the patient touching your finger then their nose repetitively, but with your finger fixed, not as a moving target (Fig. 3.32A).
- Assess rapid movements by asking the patient to twist their hand, as when turning a doorknob, and to tap the back of their hand quickly (and then rapid alternating movements by turning it over and back again quickly). Look for dysdiadochokinesis.
- Assess heel–shin coordination (Fig. 3.32B).
- Gait, discussed separately, is crucial to the assessment of coordination.

Cerebellar disease

Incoordination in PACES is usually the result of cerebellar disease (Box 3.26).

Movement disorders

Types of movement disorder are listed in Table 3.27.

Dystonia

If there is focal pathology it tends to be found in the basal ganglia (putamen) or midbrain. The most common dystonia is primary torsion dystonia (PTD). Tests to exclude a secondary cause (e.g. Wilson's disease) should be considered in young patients, those with generalised dystonia and those with features not seen in PTD, such as additional neurological signs. Types of dystonia are listed in Table 3.28. A rare group of genetic paroxysmal dyskinesias may be dystonic or choreic and include paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic

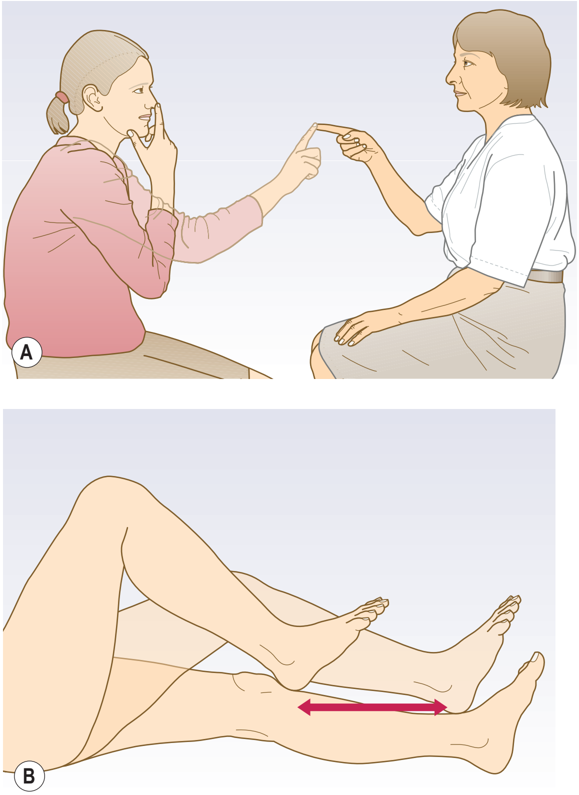


Figure 3.32 Finger–nose (A) and heel–shin (B) testing.

Box 3.26 **Cerebellar signs**

A mnemonic for the typical 'syndrome' of cerebellar signs is DASHING:

- **D**ysdiadochokinesis with rapid alternating movements
- **A**taxia of limbs and action tremor
- **S**lurred speech
- **H**eel–shin ataxia
- **I**nability to judge distance (dysmetria) with past pointing
- **N**ystagmus
- **G**ait wide based.

Note in Figure 3.31 how unilateral cerebellar disease causes ipsilateral signs. A cerebellar hemisphere feeds information to the contralateral cerebral hemisphere but then that cerebral hemisphere exerts control of movement back on the opposite side. Midline (vermis) lesions cause midline or truncal ataxia. Gait is broad based and the patient is unable to tandem-walk or stand like a flamingo! They might even be unable to sit up without falling to one side. Cerebellar hemisphere lesions cause appendicular or limb ataxia. These principles may suggest whether cerebellar pathology is unilateral or bilateral, midline, hemispheric or pancerebellar. This should narrow the differential diagnosis to structural lesions or more generalised insults.

Table 3.27 Types of movement disorder

Type of movement disorder	Clinical features
Akinetic–rigid syndromes / Parkinsonism	Clinical syndromes with bradykinesia as the defining feature, almost always accompanied by rigidity and often by tremor. Parkinsonism is discussed in Case 3.32
Tremor	A rhythmic oscillation of a body part produced by alternating or synchronous contraction of antagonistic muscles All tremors are worse with performance, anxiety and tiredness and are subdivided into predominantly rest, action or postural tremors. While resting tremors can be due to many diseases, especially of the basal ganglia, action tremors usually imply cerebellar disease; a postural tremor characterises essential tremor. To see whether the tremor is truly an action tremor, lie the patient on the bed with arms fully supported to abolish any muscle activation; a cerebellar tremor disappears. A further way to assess subtle tremor is to observe writing or drawing, e.g. an Archimedes spiral. Tremors are further discussed in Case 2.19
Dystonia (athetosis is an obsolete term for dystonia)	Sustained muscle contraction leading frequently to twisting and repetitive movements or abnormal postures
Chorea	Involuntary or semi-purposive abrupt, irregular and random movements Usually affect face, hands and feet, i.e. usually distal Large-amplitude movements (ballismus) are disabling but mild chorea is easy to miss
Myoclonus	Brief, sudden, shock-like jerks due to active muscle contraction Sudden pauses are termed 'asterixis' Causes include epilepsy, anoxia, encephalitis and prion disease
Tic	Rapid, brief jerk or sound Usually affects head or arms Suppressible at expense of tension and distress

Table 3.28 Types of dystonia

Type of dystonia	Features and causes
Focal	Focal involvement, e.g. cervical dystonia (spasmodic torticollis), blepharospasm (involuntary spasm of eye closure), oromandibular dystonia, laryngeal dystonia, brachial dystonia (writer's cramp) and foot dystonia
Segmental	Adjacent regions affected, e.g. cranial + oromandibular +/− cervical dystonia
Generalised	Legs and other areas usually affected
Hemidystonia	Unilateral dystonia to a lesion in the contralateral basal ganglia

Box 3.27 **Drug-induced movement disorders**

Dyskinesia

Dyskinesia strictly means disordered movement but the term is often used synonymously with drug-induced chorea and dystonia that occur, for example, in the later stages of Parkinson's disease.

Acute dystonia

Prochlorperazine, metoclopramide and antipsychotic drugs can produce sudden, severe dystonia, often of the head or neck. Oculogyric crises may occur. Treatment is with an intravenous anticholinergic drug (e.g. procyclidine).

Tardive dyskinesia

Continuous involuntary movements are common with long-term antipsychotics, and difficult to treat.

dyskinesia, paroxysmal exercise-induced dyskinesia and paroxysmal hypnogenic dyskinesia, some linked to writer's cramp.

Drug-induced movement disorders

These are outlined in Box 3.27.

Summary

A summary of the coordination examination sequence is given in the Summary box.

SUMMARY BOX – COORDINATION EXAMINATION SEQUENCE

- ◆ Look for nystagmus.
- ◆ Ask the patient to hold their arms outstretched and close their eyes, looking for any oscillation.
- ◆ Ask the patient to touch your finger, held out about arm's length away. Look for an intention tremor or overshoot (past pointing).
- ◆ Assess rapid movements by asking the patient to twist their hand, as when turning a doorknob, and to tap the back of their hand quickly (and then rapid alternating movements by turning it over and back again quickly).
- ◆ Look for dysdiadochokinesis.
- ◆ Assess heel–shin coordination.
- ◆ Assess gait.

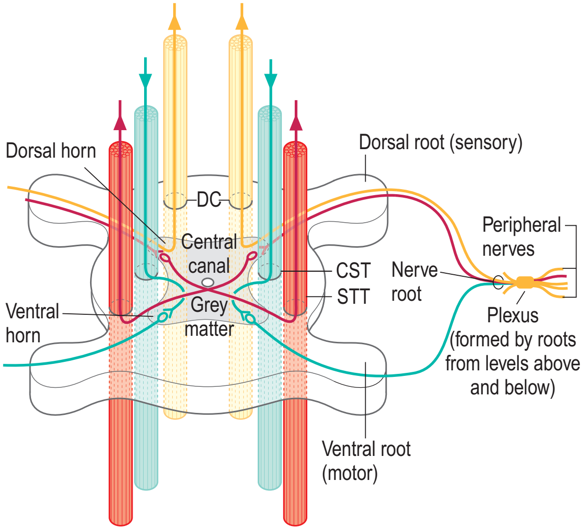


Figure 3.33 The long tracts – cross-section of one level of the spinal cord, showing the major tracts running up and down it and fibres that connect with a nerve root at that level. CST, corticospinal tracts; DC, dorsal columns; STT, spinothalamic tracts.

EXAMINATION OF POWER AND SENSATION – OVERVIEW

The spinal cord

The spinal cord

The spinal cord extends from behind the C1 vertebral body to the lower end of the L1 vertebra. A cord level is thus above its designated vertebral root exit site (Fig. 3.80, page 578). The cord is encased by the pia, subarachnoid space, arachnoid, potential dural space and dura, and supplied by branches of the vertebral arteries.

Long tracts

Knowledge of the long tracts of the spinal cord (Fig. 3.33) is essential to knowing what you are looking for when examining power and sensation in the limbs and trunk.

■ **Motor (descending) tracts.** The *corticospinal tracts* (CSTs) run downwards and throw off fibres to ventral horn cells. Arm fibres run medially to leg fibres. The CST supplying each side of the body in fact divides into a lateral

CST, carrying at least 80% of fibres (decusating in the medulla), and an anterior or ventral CST, carrying less than 20% of fibres (not decussating until the spinal cord). For practical purposes, the CST is considered here as one lateral tract.

■ **Sensory (ascending) tracts.** The *dorsal* or posterior columns (DCs) relay *proprioception* (joint position sense) and *vibration* sense from peripheral nerves, roots and dorsal horns, along their gracile (arm) and cuneate (leg) fibres. These fibres synapse in the brainstem then cross, or decussate, from the brainstem to the contralateral thalamus and sensory cortex. If a dog rubs its nose up your leg sequential segments of cortical representation or homunculus (Fig. 3.68, p. 534) will be stimulated and each will inform you exactly where its nose is. The *spinothalamic tracts* (STTs) rapidly convey *pain* and *temperature* (and some *light touch*) information to the contralateral sensory cortex but cross early, either immediately or within a few segments in the spinal cord. STTs are fast pathways. The differential crossing of DCs and STTs accounts for the signs in Brown–Séquard syndrome.

Spinal cord lesions and radiculopathies

The level of a cord lesion or the presence of a radiculopathy (root lesion) can be determined by knowledge of root myotomes and dermatomes (Box 3.28, Fig. 3.34). Power is most easily assessed in the limbs but sensation can be assessed in the limbs and trunk.

The limbs

Rapid examination screen

In the upper limbs, rapid inspection for wasting then testing for weakness of shoulder abduction, wrist extension and finger extension should detect subtle upper motor neuron weakness, proximal weakness due to a proximal myopathy and distal weakness due to a lower motor neuron lesion. In the lower limbs hip flexion and ankle dorsiflexion are the most discriminatory tests of power. Sensation can be left until last when findings should be predictable from the pattern of weakness.

Box 3.28 **Spinal cord lesions and radiculopathies**

Spinal cord lesions

In a complete spinal cord lesion there is spastic weakness of all muscle groups below the level of the lesion. There is sensory loss in all areas below the level of the lesion if sensory tracts are also involved.

Sometimes only one-half of the cord is damaged (hemisection, or Brown–Séquard syndrome) with ipsilateral weakness, and the sensory loss is said to be dissociated: ipsilateral loss of sensation carried by the dorsal columns and contralateral loss of sensation carried by the spinothalamic tracts.

Further, there may be detectable lower motor neuron myotomal weakness at the level of a lesion if there is damage to the ventral horn cell or ventral nerve root at that level.

In T2–L1 lesions all muscle groups in the lower limbs are spastic and testing power has no localising value. Seeking where trunk dermatomal sensory loss (below) starts is the most effective way of assessing the level of thoracic spine lesions. Abdominal reflexes are easy to understand when you think of a ‘tummy tickle’. The tickly feeling is due to stimulation of the lower thoracic sensory fibres T8–12 and is lost in lower thoracic lesions. In lumbar, sacral and cervical lesions identifying dermatomal loss helps determine the level of the lesion. Early in disease there may be considerable pain at the level of a lesion. When limb dermatomes are painful, spinal cord and root disease is often considered; this is not so for thoracic cord or root disease, when heart, lung and abdominal diagnoses are often considered before dermatomal pain, and thoracic root shingles or vertebral collapse easily ignored.

Radiculopathies

In a radiculopathy there is discrete myotomal weakness and dermatomal sensory loss.

The term myotome refers to the muscles supplied by a particular nerve root, no matter how the nerve fibres within that root are finally distributed via the limb plexuses and peripheral nerves. In root lesions, affected muscles are weak and flaccid, and any reflexes involving that root are lost.

The term dermatome refers to the area of skin supplied by a nerve root (Fig. 3.34). Dermatomes vary between individuals and overlap in individuals.

Myotomes

Movements supplied by specific roots are:

- C5 – shoulder abduction (+ biceps reflex)
- C6 – elbow flexion (+ supinator reflex)
- C7 – elbow extension (+ triceps reflex)
- C8 – finger flexion and extension
- T1 – movements of the small muscles of the hand
- L2 – hip flexion / adduction
- L3 – knee extension (+ knee reflex)
- L4 – ankle inversion (+ knee reflex)
- L5 – ankle dorsiflexion
- S1 – ankle plantar flexion / eversion (+ ankle reflex).

Generally two, and sometimes more, roots contribute to a particular movement, but one (listed above) makes the major contribution. Reference sources vary in ascribing nerve roots to particular movements, and in reality there is considerable biological variation between individuals. There are eight cervical roots but seven vertebrae. Root C1 exits above the C1 vertebra and C8 below the C7 vertebra. All thoracic and lumbar roots exit below their designated vertebra and sacral roots from foramina in the coccyx. Lumbar and sacral roots travel a long distance from their cord segment of origin to their exit site.

Dermatomes

Dermatomes are shown in Figure 3.34.

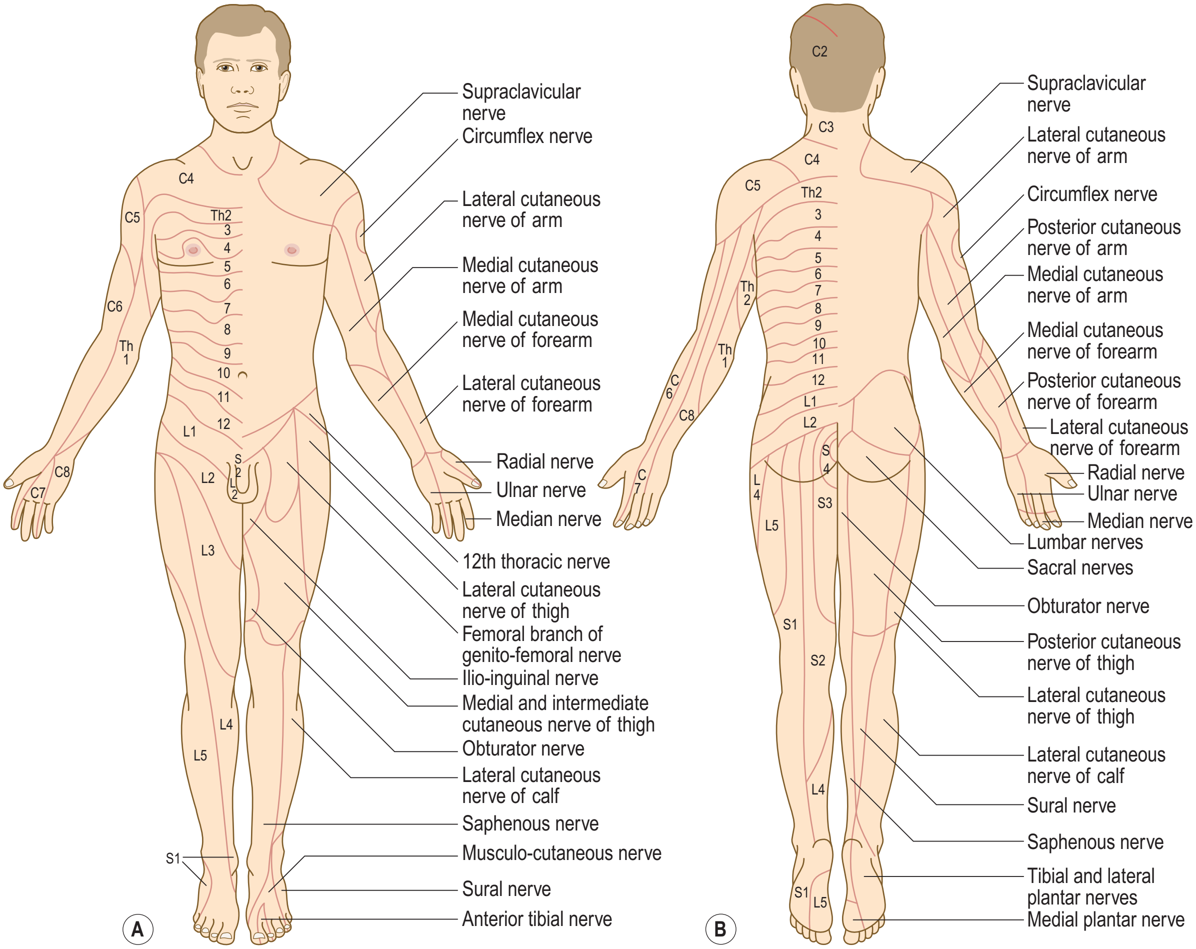

Supraclavicular nerve
Circumflex nerve
Lateral cutaneous nerve of arm
Medial cutaneous nerve of arm
Medial cutaneous nerve of forearm
Lateral cutaneous nerve of forearm
Radial nerve
Ulnar nerve
Median nerve
12th thoracic nerve
Lateral cutaneous nerve of thigh
Femoral branch of genito-femoral nerve
Ilio-inguinal nerve
Medial and intermediate cutaneous nerve of thigh
Obturator nerve
Lateral cutaneous nerve of calf
Saphenous nerve
Musculo-cutaneous nerve
Sural nerve
Anterior tibial nerve
C4
C5
C6
C7
C8
Th2
3
4
5
6
7
8
9
10
11
12
Th 1
L1
L2
L3
L4
L5
S 2
L 2
S1
A
C2
C3
C4
C5
Th2
Th 2
Th 1
C 6
C8
C 7
L1
L2
L 4
L5
S 4
S3
S1
S2
L4
S1
L5
B
Supraclavicular nerve
Lateral cutaneous nerve of arm
Circumflex nerve
Posterior cutaneous nerve of arm
Medial cutaneous nerve of arm
Medial cutaneous nerve of forearm
Posterior cutaneous nerve of forearm
Lateral cutaneous nerve of forearm
Radial nerve
Ulnar nerve
Median nerve
Lumbar nerves
Sacral nerves
Obturator nerve
Posterior cutaneous nerve of thigh
Lateral cutaneous nerve of thigh
Lateral cutaneous nerve of calf
Sural nerve
Saphenous nerve
Tibial and lateral plantar nerves
Medial plantar nerve

Figure 3.34 Dermatomes.

Examining power

Whilst the above is a useful screen when you do not suspect neurological disease, a more complete examination is required in neurological cases. *The key to examining the limbs is in examining power.*

■ **Grading power.** There are numerous ways of grading power (Table 3.29), but it is also useful to describe weakness in terms of functional loss.

■ **Five patterns of weakness.** It is important diagnostically to consider *five patterns of weakness* (Table 3.30). Each has *characteristic signs*. Recognising the pattern offers a *clinical correlate*. The clinical correlate connects the site of the lesion, determined from the pattern of weakness, to *numerous possible pathologies or diagnoses*. Generally, reaching the clinical correlate is by clinical examination and determining the pathology by history and investigation. When examining limbs, aim to identify the clinical correlate before considering possible diagnoses.

Table 3.29 Medical Research Council grading of power

Grade	Definition
5	Normal
4	Active movement against gravity and resistance but not full strength
3	Active movement against gravity but not against resistance
2	Active movement with gravity eliminated
1	Flicker of movement on voluntary contraction
0	No visible or palpable movement

Sometimes multiple patterns of weakness occur, e.g. cervical myeloradiculopathy, cervical myelopathy with peripheral neuropathy, diabetic peripheral neuropathy with mononeuritis multiplex.

Table 3.30 Five patterns of weakness

	Pattern of weakness	Characteristic signs	Clinical correlate	Possible pathologies or diagnoses
Upper motor neuron weakness	All muscle groups in the arm, leg or both (although arm flexors tend to be stronger than extensors and leg extensors stronger than leg flexors) But note that isolated bits of limb may be affected if only a small part of the homunculus is damaged (Fig. 3.69, Case 3.27); this may be especially so higher in the cortex where fibres travelling to and from their destined home on the homunculus map are more sparsely populated, whereas lower in the cortex they have all bunched together; it is analogous to rural living high in the cortex, before they head to work on the motorway that is ultimately the internal capsule	Increased tone or spasticity Enhanced reflexes Extensor (upgoing) plantar response	Monoparesis (one limb)	Stroke
			Hemiparesis (arm and leg on one side)	Internal capsule stroke (e.g. + upper motor neuron facial weakness ipsilateral to hemiparesis) Brainstem stroke (e.g. + cranial neuropathies contralateral to hemiparesis)
			Tetra(quadri)paresis (all four limbs, e.g. high cervical cord lesion, bilateral brainstem or cerebral hemisphere lesions)	Cervical myelopathy
			Paraparesis (both legs due to spinal cord disease below the level of the arms)	Demyelination
Lower motor neuron weakness – focal	Weakness due to disease in spinal nerve (root), nerve plexus (web of neurons with fibres from different roots) or specific peripheral nerve Site of weakness depends on the root, plexus or nerve affected. Specific myotomal patterns of weakness and dermatomal patterns of sensory loss are associated with root lesions (Box 3.28). Specific weakness and sensory loss occur in specific nerve lesions. Patchy signs may occur with multiple nerve lesions (mononeuritis multiplex)	Wasting (+/– fasciculation) Flaccid tone Attenuated reflexes (in affected muscle groups)	Radiculopathy	Box 3.28
			Plexopathy	Brachial plexopathy in Pancoast's syndrome
			Mononeuropathy	Carpal tunnel syndrome Ulnar nerve palsy Radial nerve palsy Common peroneal nerve palsy
			Mononeuritis multiplex	Diabetes Vasculitis
Lower motor neuron weakness – diffuse and distal	Symmetrical weakness in all muscle groups distally	Multiple nerve tips are involved and weakness, sensory loss and reflex loss start at the feet and ankles and ascend (fingertips starting to be affected by the time disease reaches knees)	Peripheral neuropathy	Many causes, some predominantly sensory, some motor and some both
Neuromuscular junction weakness	Muscular weakness	Muscle weakness – limbs, bulbar, ptosis Fatigability (muscles becoming weaker with activity)	Myasthenia	Myasthenia
Muscle weakness	Symmetrical weakness in all muscle groups, (usually) proximally	No other neurological signs	Myopathy Dystrophy	Many causes

Examining tone

A little resistance is normal. Increased tone is due to upper motor neuron lesions. Increased tone due to *spasticity* is best elicited by rapid movements and is present if resistance increases suddenly ('the catch' or clasp-knife), e.g. the heel flings up from the bed when the knee is lifted quickly. *Lead-pipe rigidity* is when tone is increased throughout movement. Extrapyramidal *cogwheel rigidity*, with regular intermittent breaks, is best elicited by slow movements. *Paratonia* or *Gegenhalten* refers to resistance due to frontal lobe damage and is common in cerebrovascular disease. Flaccid tone, with loss of resistance throughout movements, indicates lower motor neuron lesions. The heel does not lift off the bed when the knee is lifted quickly.

Examining reflexes

Reflexes are monosynaptic responses to the stretch of muscle fibres, mediated in the spinal cord. Reflexes and tone have a further inhibitory input from higher neurons in the muscles they supply. In lower motor neuron lesions, reflexes are reduced or absent. In upper motor neuron lesions there is disinhibition from higher neurons and reflexes are increased. Always use a long tendon hammer, and let it swing with its own weight onto the muscle. Patients should be relaxed, which is best achieved by not telling them to relax! Reflexes are graded as in Box 3.29.

Increased reflexes occur in upper motor neuron lesions. Absent or reduced (more difficult to judge) reflexes occur in lower motor neuron lesions. The term inverted reflex merely implies the absence of a reflex at one, or sometimes more, level (e.g. C5 and C6) and brisk reflexes below and indicates a spinal cord lesion at the level of the absent reflexes.

Examining sensation

Usually, examiners will stop you before you embark on sensory examination. The exceptions are with a radiculopathy, a specific mononeuropathy or peripheral neuropathy. The modalities to test for are proprioception (joint position sense), vibration, temperature and pinprick.

■ **Proprioception.** Grasping the sides of a finger or big toe, move it up and down, demonstrating to the patient, before asking them to close their eyes and report the direction of movement being applied (Fig. 3.35).

■ **Vibration.** A 128 Hz tuning fork may be applied over the first metatarsophalangeal joints, medial malleoli, knee, greater trochanters, anterior superior iliac spines, ribs, sternum, wrists, elbows and shoulders (Fig. 3.36)

Box 3.29 **Grading reflexes**

– Absent
+– Present only with reinforcement
+ Diminished
++ Normal
+++ Hyperactive
++++ Clonus

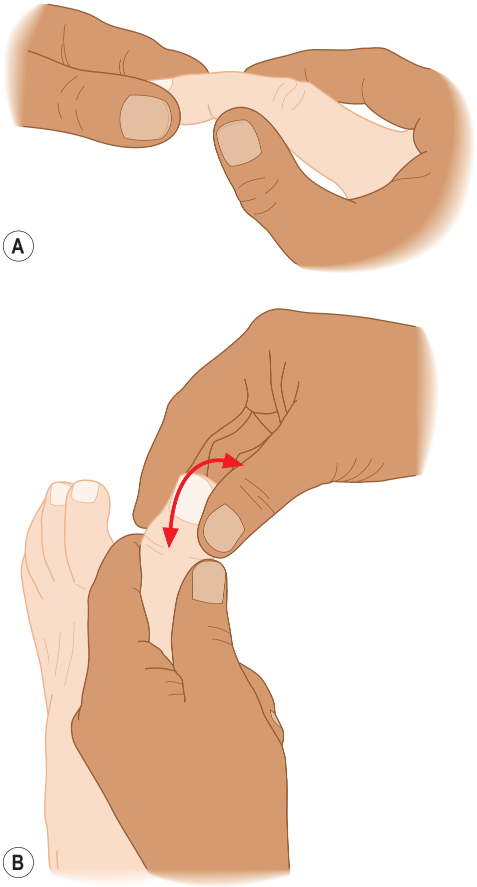


Figure 3.35 Testing proprioception in finger (A) and toe (B).

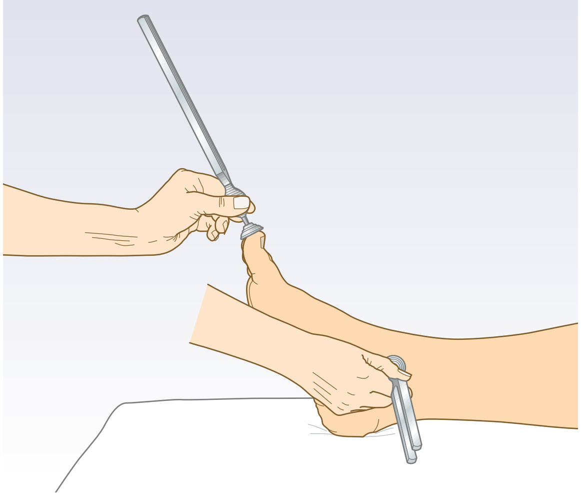


Figure 3.36 Testing vibration sense.

Table 3.31 Patterns of sensory loss

Lesion	Pattern of sensory loss
Parietal lobe lesion	Sensory inattention or neglect Recognition of all types of sensation may be intact, but poor localisation – two-point discrimination lost
Thalamic lesion	Hemisensory loss of all modalities of sensation
Brainstem lesion	Loss of pain and temperature on face and opposite side of body in lateral medullary syndrome
Spinal cord lesions	
Complete transverse lesion	Complete loss of all sensory modalities below lesion
Brown–Séquard hemisection	Loss of pain and temperature sensation contralaterally and proprioception and vibration sense ipsilaterally below lesion
Central cord lesion, e.g. syringomyelia	Loss of pain and temperature sensation bilaterally below lesion with other modalities preserved (dissociated sensory loss)
Dorsal column lesion, e.g. tabes dorsalis	Loss of proprioception and vibration sense bilaterally below lesion
Anterior spinal syndrome	Loss of pain and temperature sensation bilaterally below lesion with preserved proprioception and vibration sense
Radiculopathy	Dermatomal loss
Mononeuropathy	Sensory loss in distribution of nerve
Peripheral neuropathy	Peripheral symmetrical sensory loss

■ **Temperature.** A cold tuning fork tests the spinothalamic tracts.

■ **Light touch and pinprick.** Using a disposable neurological pin, first confirm on the patient's sternum that the difference between sharp and blunt is appreciated. Light touch may also be assessed, with cotton wool, and not a stroking movement. 'Light' is the operative word – many candidates apply touch that pachyderms such as elephants or hippos would detect!

Pinprick and light touch loss are often the first to be noticed by patients but the other sensory modalities may be more discriminating. For all sensory modalities you can interpret patterns of sensory loss (Table 3.31).

EXAMINATION OF THE UPPER LIMBS

Inspection

Note any obvious wasting, fasciculation, tremor or unusual posture. The face may reveal asymmetry, wasting, a Parkinsonian expression, Horner's syndrome, nystagmus and so on.

Tone

Take the hand as if to shake it and hold the forearm. Pronate and supinate the forearm, then roll the hand at the wrist and finally flex and extend the elbow. Repeat movements at different speeds.

Power

Instruct the patient 'Hold your arms out in front of you and close your eyes' and look for:

- Upper motor neuron weakness (the arm falls)
- Drift (the arm wanders in the presence of a parietal lesion)
- Overshoot (when the arm is tapped with eyes closed it fails to rediscover its point of origin) and the action tremor of cerebellar disease.

If there is an obvious upper motor neuron weakness it is not necessary to examine every muscle group. Full examination would begin by asking the patient to shrug their shoulders adducting the scapulae (C3,4 roots and trapezius muscles), brace back their shoulders (C4,5 roots and rhomboids) and push forward against resistance (C5–7 roots and serratus anterior muscles) but these instructions are seldom necessary.

Examining shoulder movements

Refer to Figure 3.37.

Examining elbow movements

Refer to Figure 3.38.

Examining wrist movements

Refer to Figure 3.39.

Examining finger movements (that do not involve small muscles of the hand)

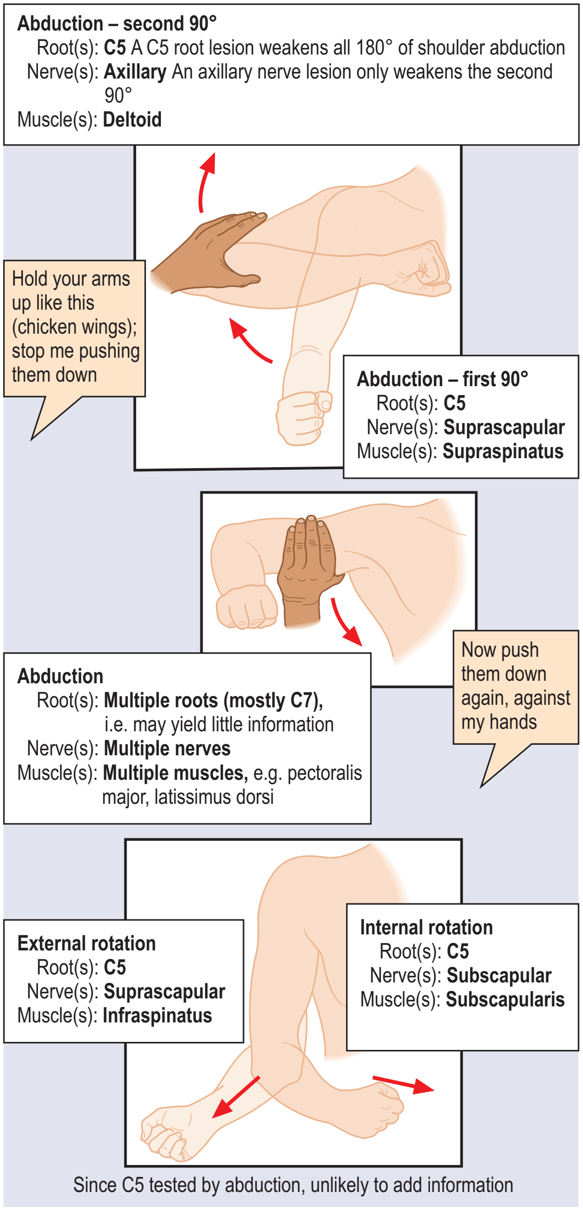
Refer to Figure 3.40.

Examining the small (intrinsic) muscles of the hand

Refer to Figure 3.41. These muscles all originate within the hand and are supplied from the T1 nerve roots via the median and ulnar nerves. The median nerve supplies just four small muscles ('LOAF' – lateral two lumbricals, opponens pollicis, abductor pollicis brevis, flexor pollicis brevis, which are the thenar muscles) and the ulnar nerve supplies all other small muscles – hypothenar muscles, medial two lumbricals, interossei which abduct and adduct the fingers, and adductor pollicis.

Reflexes

With the patient's arms relaxed and rested lightly on the abdomen, test the upper limb reflexes (Fig. 3.42).



Abduction – second 90°
Root(s): **C5** A C5 root lesion weakens all 180° of shoulder abduction
Nerve(s): **Axillary** An axillary nerve lesion only weakens the second 90°
Muscle(s): **Deltoid**

Hold your arms up like this (chicken wings); stop me pushing them down

Abduction – first 90°
Root(s): **C5**
Nerve(s): **Suprascapular**
Muscle(s): **Supraspinatus**

Now push them down again, against my hands

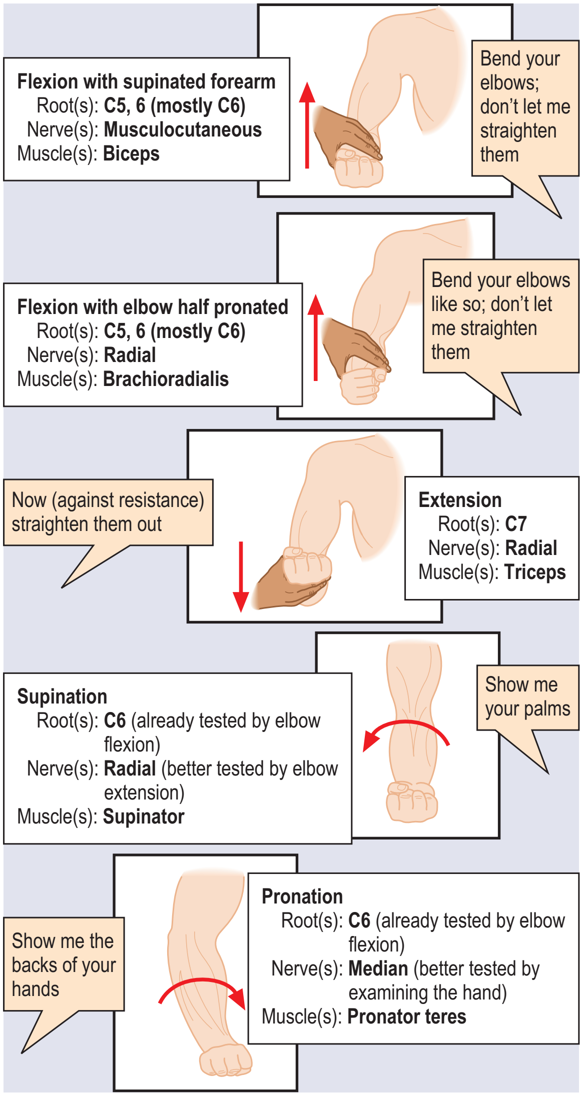
Abduction
Root(s): **Multiple roots (mostly C7),** i.e. may yield little information
Nerve(s): **Multiple nerves**
Muscle(s): **Multiple muscles,** e.g. pectoralis major, latissimus dorsi

External rotation
Root(s): **C5**
Nerve(s): **Suprascapular**
Muscle(s): **Infraspinatus**

Internal rotation
Root(s): **C5**
Nerve(s): **Subscapular**
Muscle(s): **Subscapularis**

Since C5 tested by abduction, unlikely to add information

Figure 3.37 Examining shoulder movements.



Flexion with supinated forearm
Root(s): **C5, 6 (mostly C6)**
Nerve(s): **Musculocutaneous**
Muscle(s): **Biceps**

Bend your elbows; don't let me straighten them

Flexion with elbow half pronated
Root(s): **C5, 6 (mostly C6)**
Nerve(s): **Radial**
Muscle(s): **Brachioradialis**

Bend your elbows like so; don't let me straighten them

Now (against resistance) straighten them out

Extension
Root(s): **C7**
Nerve(s): **Radial**
Muscle(s): **Triceps**

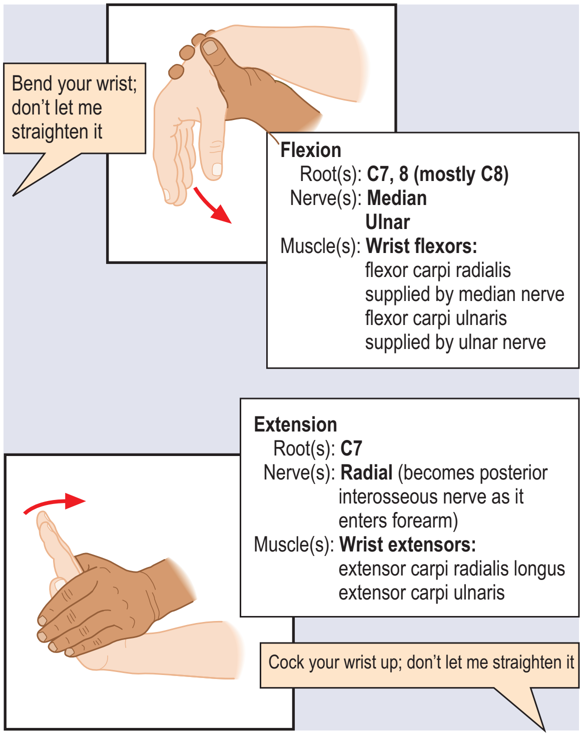
Supination
Root(s): **C6** (already tested by elbow flexion)
Nerve(s): **Radial** (better tested by elbow extension)
Muscle(s): **Supinator**

Show me your palms

Show me the backs of your hands

Pronation
Root(s): **C6** (already tested by elbow flexion)
Nerve(s): **Median** (better tested by examining the hand)
Muscle(s): **Pronator teres**

Figure 3.38 Examining elbow movements.



Bend your wrist; don't let me straighten it

Flexion
Root(s): **C7, 8 (mostly C8)**
Nerve(s): **Median**
Ulnar
Muscle(s): **Wrist flexors:**
flexor carpi radialis supplied by median nerve
flexor carpi ulnaris supplied by ulnar nerve

Extension
Root(s): **C7**
Nerve(s): **Radial** (becomes posterior interosseous nerve as it enters forearm)
Muscle(s): **Wrist extensors:**
extensor carpi radialis longus
extensor carpi ulnaris

Cock your wrist up; don't let me straighten it

Figure 3.39 Examining wrist movements.

Coordination

A rapid finger–nose test should tell you whether or not to pursue cerebellar examination as outlined in 'Examining coordination.'

Sensation

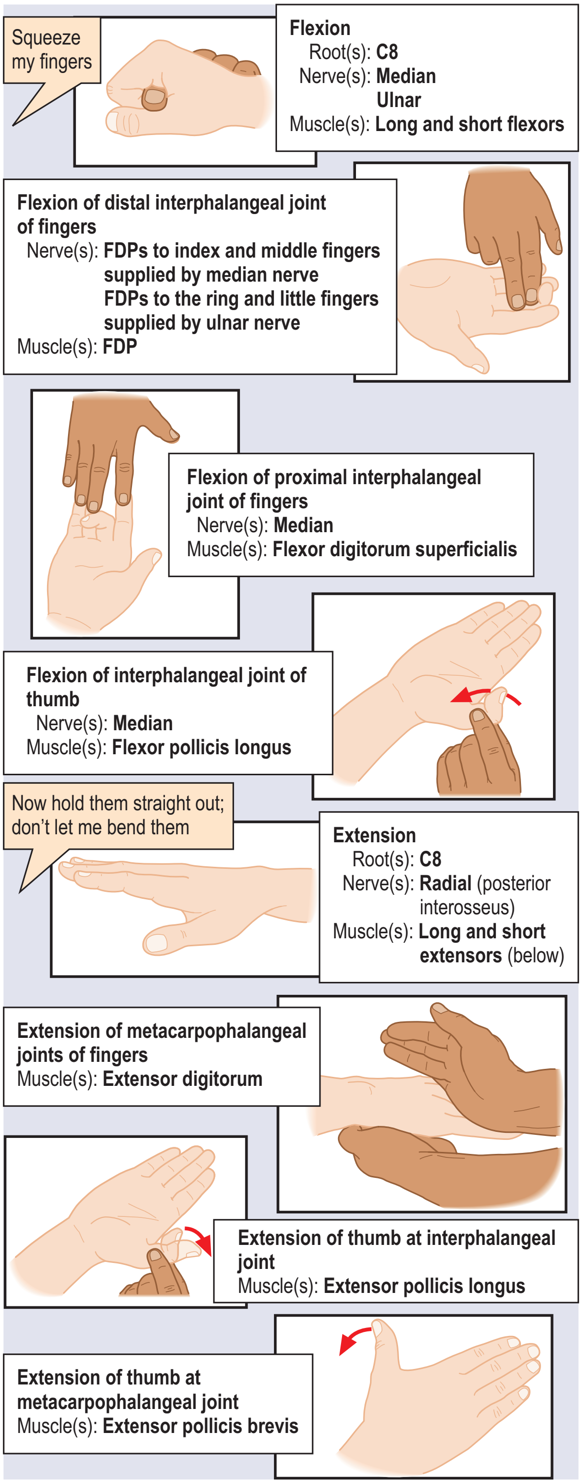
Refer to 'Examining power and sensation – overview'.

Summary

A summary of the upper limb examination sequence is given in the Summary box.

SUMMARY BOX – UPPER LIMB EXAMINATION SEQUENCE

- Look for wasting, fasciculation, tremor or unusual posture.
- Assess tone.
- Examine shoulder movements (Fig. 3.37).
- Examine elbow movements (Fig. 3.38).
- Examine wrist movements (Fig. 3.39).
- Examine finger movements (Fig. 3.40).
- Examine the small muscles of the hand (Fig. 3.41).
- Examine biceps, triceps and supinator reflexes.
- Examine coordination with a rapid finger–nose test.
- Examine sensation.



Squeeze my fingers

Flexion
Root(s): **C8**
Nerve(s): **Median**
Ulnar
Muscle(s): **Long and short flexors**

Flexion of distal interphalangeal joint of fingers
Nerve(s): **FDPs to index and middle fingers supplied by median nerve**
FDPs to the ring and little fingers supplied by ulnar nerve
Muscle(s): **FDP**

Flexion of proximal interphalangeal joint of fingers
Nerve(s): **Median**
Muscle(s): **Flexor digitorum superficialis**

Flexion of interphalangeal joint of thumb
Nerve(s): **Median**
Muscle(s): **Flexor pollicis longus**

Now hold them straight out; don't let me bend them

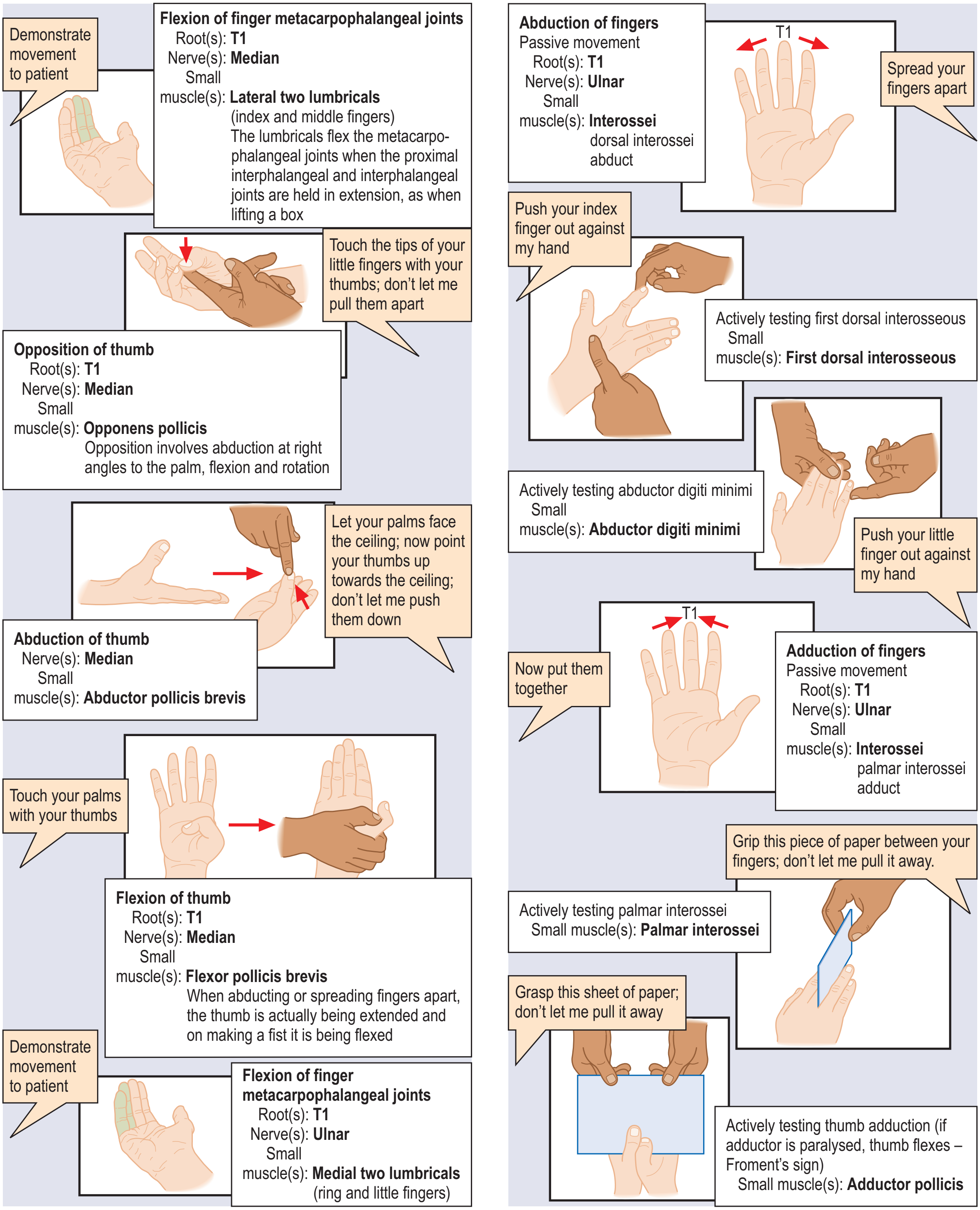
Extension
Root(s): **C8**
Nerve(s): **Radial** (posterior interosseus)
Muscle(s): **Long and short extensors** (below)

Extension of metacarpophalangeal joints of fingers
Muscle(s): **Extensor digitorum**

Extension of thumb at interphalangeal joint
Muscle(s): **Extensor pollicis longus**

Extension of thumb at metacarpophalangeal joint
Muscle(s): **Extensor pollicis brevis**

Figure 3.40 Examining finger movements. FDP, flexor digitorum profundus.



Demonstrate movement to patient

Flexion of finger metacarpophalangeal joints
Root(s): **T1**
Nerve(s): **Median**
Small muscle(s): **Lateral two lumbricals** (index and middle fingers)
The lumbricals flex the metacarpophalangeal joints when the proximal interphalangeal and interphalangeal joints are held in extension, as when lifting a box

Touch the tips of your little fingers with your thumbs; don't let me pull them apart

Opposition of thumb
Root(s): **T1**
Nerve(s): **Median**
Small muscle(s): **Opponens pollicis**
Opposition involves abduction at right angles to the palm, flexion and rotation

Let your palms face the ceiling; now point your thumbs up towards the ceiling; don't let me push them down

Abduction of thumb
Nerve(s): **Median**
Small muscle(s): **Abductor pollicis brevis**

Touch your palms with your thumbs

Flexion of thumb
Root(s): **T1**
Nerve(s): **Median**
Small muscle(s): **Flexor pollicis brevis**
When abducting or spreading fingers apart, the thumb is actually being extended and on making a fist it is being flexed

Demonstrate movement to patient

Flexion of finger metacarpophalangeal joints
Root(s): **T1**
Nerve(s): **Ulnar**
Small muscle(s): **Medial two lumbricals** (ring and little fingers)

Abduction of fingers
Passive movement
Root(s): **T1**
Nerve(s): **Ulnar**
Small muscle(s): **Interossei**
dorsal interossei abduct

Spread your fingers apart

Push your index finger out against my hand

Actively testing first dorsal interosseous
Small muscle(s): **First dorsal interosseous**

Actively testing abductor digiti minimi
Small muscle(s): **Abductor digiti minimi**

Push your little finger out against my hand

Now put them together

Adduction of fingers
Passive movement
Root(s): **T1**
Nerve(s): **Ulnar**
Small muscle(s): **Interossei**
palmar interossei adduct

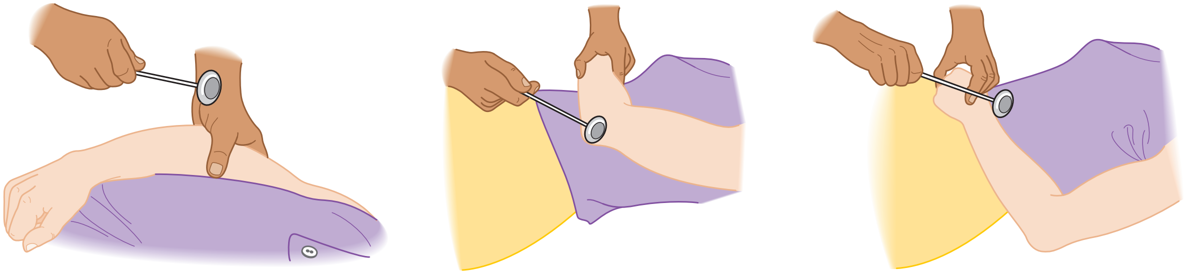
Grip this piece of paper between your fingers; don't let me pull it away.

Actively testing palmar interossei
Small muscle(s): **Palmar interossei**

Grasp this sheet of paper; don't let me pull it away

Actively testing thumb adduction (if adductor is paralysed, thumb flexes – Froment's sign)
Small muscle(s): **Adductor pollicis**

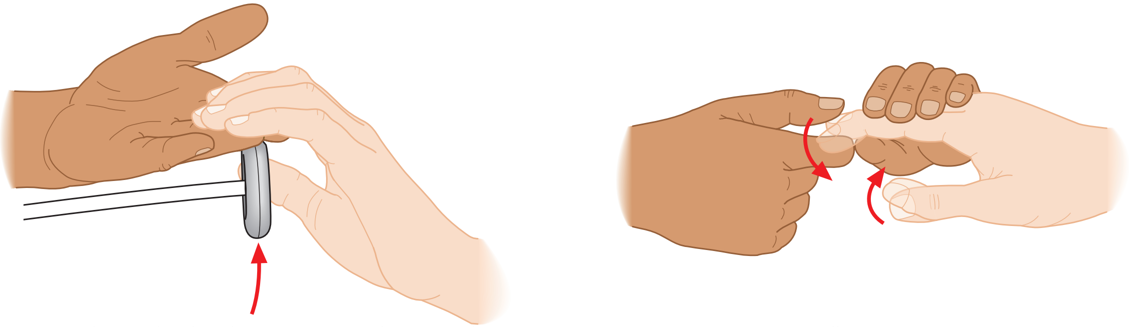
Figure 3.41 Examining the small muscles of the hand.



Eliciting the biceps reflex C5, 6 (mostly 5) – contracts via musculocutaneous nerve

Eliciting the triceps reflex C7 – contracts via radial nerve

Eliciting the supinator reflex C5, 6 (mostly 6) – slight finger and elbow flexion as brachioradialis (not supinator!) contracts via radial nerve



Eliciting the finger reflex C8 – flexor digitorum profundus and flexor digitorum superficialis contract via median and ulnar nerves

Hoffmann's sign

Figure 3.42 Testing upper limb reflexes.

EXAMINATION OF THE LOWER LIMBS

Inspection

Note any deformity or positional abnormality. Look for wasting and fasciculation.

Tone

Roll the legs, externally and internally rotating the hips (Fig. 3.43A). Flick them up from behind the knees – the heel will 'fly' if there is spasticity and remain in contact with the bed at all times if the leg is flaccid. Normally there is only minimal departure of the heel from the bed (Fig. 3.43B). Check for ankle clonus. With the knee semiflexed and the foot relaxed, suddenly pull the foot dorsally and hold it, looking for sustained contractions at the ankle joint (Fig. 3.43C). More than three beats is abnormal.

Power

The patient should be lying supine. Examine sections of the lower limbs as follows.

Examining hip movements

Refer to Figure 3.44.

Examining knee movements

Refer to Figure 3.45.

Examining ankle movements

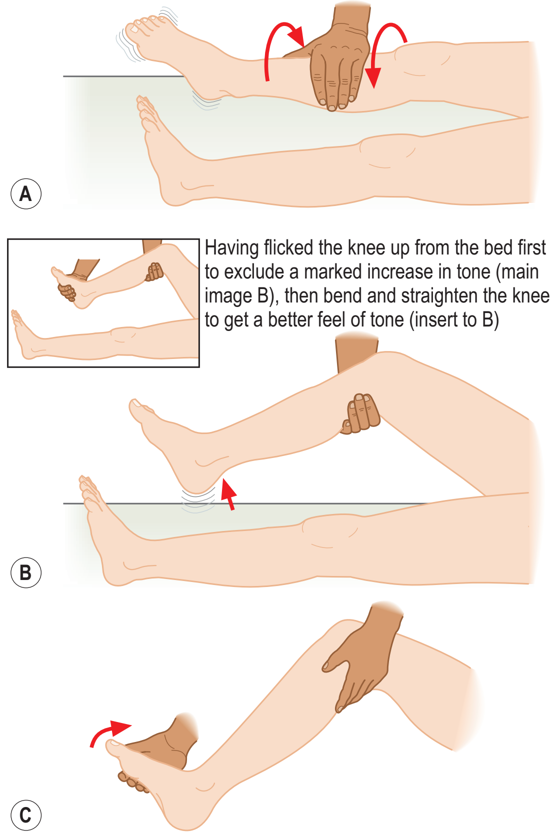
Refer to Figure 3.46. Note that the *sciatic nerve* has two divisions, the *common peroneal* (lateral popliteal) nerve and the *tibial* (medial popliteal) nerve. The *common peroneal nerve* has two subdivisions, the *deep* and *superficial* peroneal nerves.

Examining toe movements

Refer to Figure 3.47.

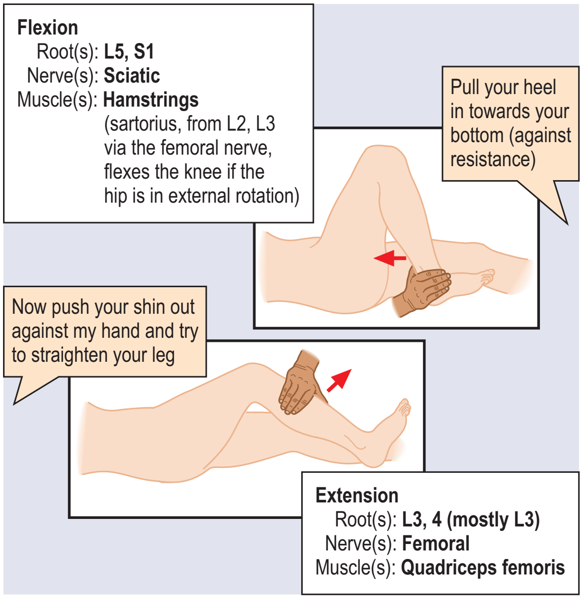
Reflexes

With the patient's legs relaxed, test the lower limb reflexes (Fig. 3.48).



Having flicked the knee up from the bed first to exclude a marked increase in tone (main image B), then bend and straighten the knee to get a better feel of tone (insert to B)

Figure 3.43 Testing tone in the lower limbs: (A) rock the leg to and fro, (B) flick the leg up from behind the knee, (C) test for ankle clonus.



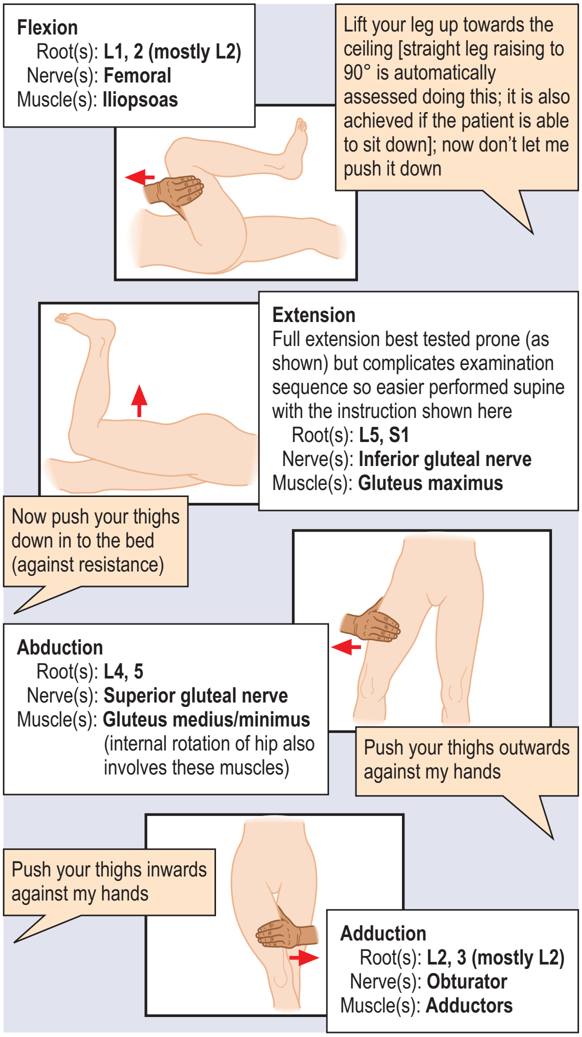
Flexion
Root(s): **L5, S1**
Nerve(s): **Sciatic**
Muscle(s): **Hamstrings** (sartorius, from L2, L3 via the femoral nerve, flexes the knee if the hip is in external rotation)

Pull your heel in towards your bottom (against resistance)

Now push your shin out against my hand and try to straighten your leg

Extension
Root(s): **L3, 4 (mostly L3)**
Nerve(s): **Femoral**
Muscle(s): **Quadriceps femoris**

Figure 3.45 Examining knee movements.



Flexion
Root(s): **L1, 2 (mostly L2)**
Nerve(s): **Femoral**
Muscle(s): **Iliopsoas**

Lift your leg up towards the ceiling [straight leg raising to 90° is automatically assessed doing this; it is also achieved if the patient is able to sit down]; now don't let me push it down

Extension
Full extension best tested prone (as shown) but complicates examination sequence so easier performed supine with the instruction shown here
Root(s): **L5, S1**
Nerve(s): **Inferior gluteal nerve**
Muscle(s): **Gluteus maximus**

Now push your thighs down in to the bed (against resistance)

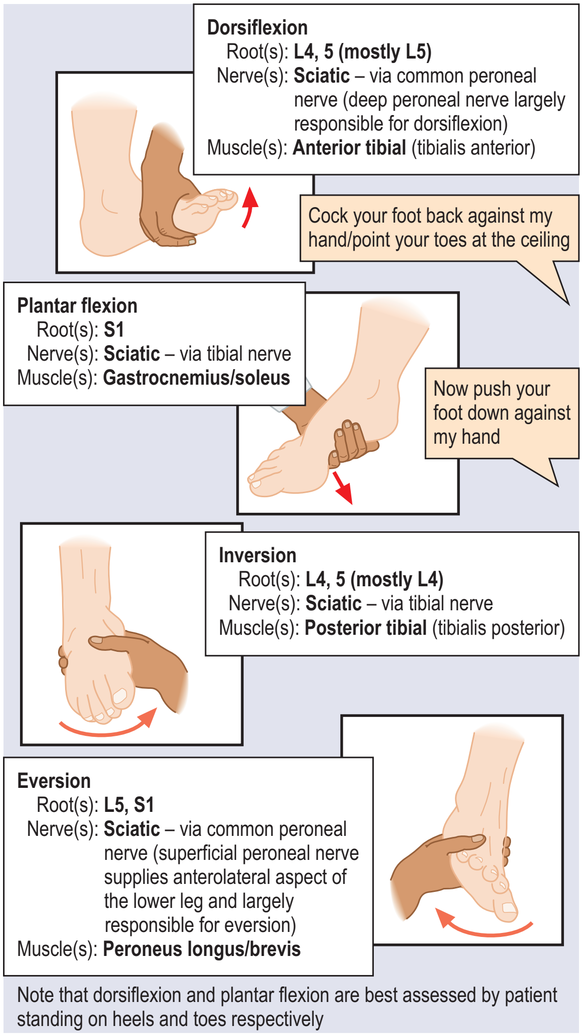
Abduction
Root(s): **L4, 5**
Nerve(s): **Superior gluteal nerve**
Muscle(s): **Gluteus medius/minimus** (internal rotation of hip also involves these muscles)

Push your thighs outwards against my hands

Push your thighs inwards against my hands

Adduction
Root(s): **L2, 3 (mostly L2)**
Nerve(s): **Obturator**
Muscle(s): **Adductors**

Figure 3.44 Examining hip movements.


Cock your foot back against my hand/point your toes at the ceiling
Now push your foot down against my hand

Dorsiflexion
Root(s): **L4, 5 (mostly L5)**
Nerve(s): **Sciatic** – via common peroneal nerve (deep peroneal nerve largely responsible for dorsiflexion)
Muscle(s): **Anterior tibial** (tibialis anterior)

Plantar flexion
Root(s): **S1**
Nerve(s): **Sciatic** – via tibial nerve
Muscle(s): **Gastrocnemius/soleus**

Inversion
Root(s): **L4, 5 (mostly L4)**
Nerve(s): **Sciatic** – via tibial nerve
Muscle(s): **Posterior tibial** (tibialis posterior)

Eversion
Root(s): **L5, S1**
Nerve(s): **Sciatic** – via common peroneal nerve (superficial peroneal nerve supplies anterolateral aspect of the lower leg and largely responsible for eversion)
Muscle(s): **Peroneus longus/brevis**

Note that dorsiflexion and plantar flexion are best assessed by patient standing on heels and toes respectively

Figure 3.46 Examining ankle movements.

Coordination

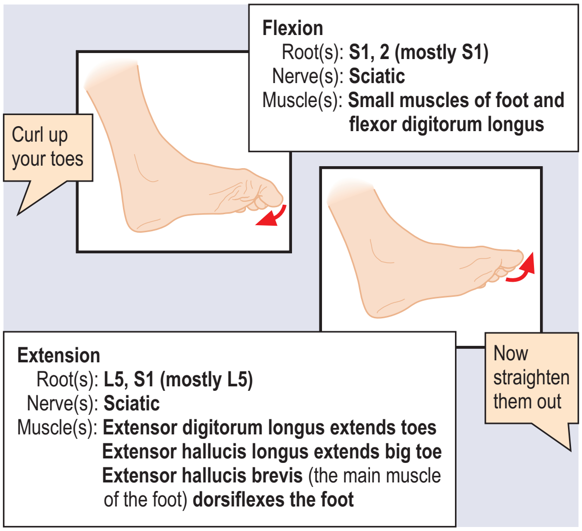
Ask the patient to run their heel smoothly up and down the shin and watch for any tremor or difficulty coordinating this movement.

Sensation

Refer to 'Examining power and sensation – overview.'

Summary

A summary of the lower limb examination sequence is in the Summary box.



Flexion
Root(s): **S1, 2 (mostly S1)**
Nerve(s): **Sciatic**
Muscle(s): **Small muscles of foot and flexor digitorum longus**

Extension
Root(s): **L5, S1 (mostly L5)**
Nerve(s): **Sciatic**
Muscle(s): **Extensor digitorum longus extends toes**
Extensor hallucis longus extends big toe
Extensor hallucis brevis (the main muscle of the foot) **dorsiflexes the foot**

Figure 3.47 Examining toe movements.

SUMMARY BOX – LOWER LIMB EXAMINATION SEQUENCE

- Look for deformity or any positional abnormality, wasting and fasciculation.
- Assess tone and examine for clonus.
- Examine hip movements (Fig. 3.44).
- Examine knee movements (Fig. 3.45).
- Examine ankle movements (Fig. 3.46).
- Examine toe movements (Fig. 3.47).
- Examine knee and ankle reflexes.
- Assess the plantar responses.
- Examine coordination with a rapid heel–shin test.
- Examine sensation.

EXAMINATION OF GAIT

Gait abnormalities

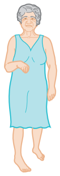
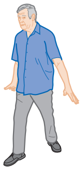
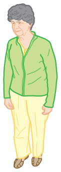
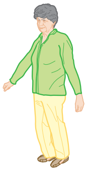
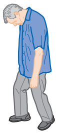
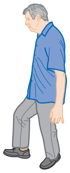
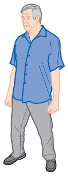
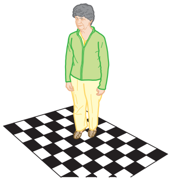
Examining gait is an essential part of lower limb and more generalised neurological examination. Common abnormal types of gait are illustrated in Table 3.32 and whilst these may become easy to recognise a suggested sequence for detecting these is given in the Summary box.

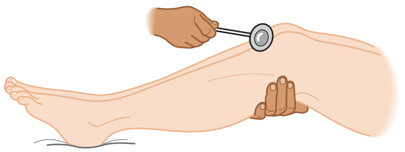
Most gaits are symmetrical. Asymmetric gaits may be due to hemiplegia, a foot drop or pain.

Summary

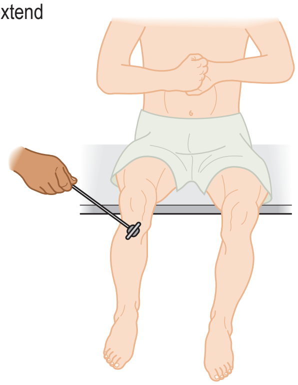
A summary of the gait examination sequence is given in the Summary box.

Table 3.32 Common abnormal types of gait

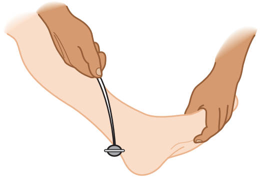
Gait	Signs	What to look for next	Possible causes
Spastic 	Awkward, as if wading through mud, with foot turned inwards May be part of hemiplegia or paraplegia – in hemiplegia pelvis on affected side tilted upwards to raise spastic leg off the floor; in paraplegia gait is scissoring, as if the legs are trying to cross over each other	Upper motor neuron signs Hemiplegia Sensory level if paraplegia	Stroke Demyelination
Cerebellar 	Wide based Lurching as if on the deck of a ship	Other cerebellar signs	Alcohol Cerebellar degeneration
Parkinsonian 	Short, shuffling steps Lack of arm swing Stooped posture as though shuffling steps are hurrying to keep up with it – so-called festinant gait	Other signs of Parkinson's disease, e.g. bradykinesia, hypomimia, rigidity, asymmetrical resting tremor	Parkinson's disease
Marche à petit pas 	Short steps Preserved arm swing Upright posture	Assess cerebrovascular risk factors	Diffuse small-vessel disease
Sensory ataxic (stamping) gait 	Foot seems to stamp down onto the floor Movements of leg(s) bear(s) no relation to its / their position in space Wide based and apprehensive, patient looking to floor to aid unsure steps	Positive Romberg's sign Impaired proprioception and vibration sense	Subacute combined degeneration of cord Tabes dorsalis Friedreich's ataxia Cervical myelopathy
High stepping 	Foot drop Patient lifts leg or bends knee to avoid forefoot scraping ground	Signs of common peroneal nerve palsy	Common peroneal nerve palsy Hereditary motor and sensory neuropathy 1 Sciatic nerve lesion L4, 5 radiculopathy
Waddling 	Wide-based gait with weight shifting from side to side of pelvis as patient waddles forwards	Inspection for likely causes of proximal myopathy, e.g. Cushing's syndrome	Cushing's syndrome Thyrotoxicosis Polymyositis
Apraxic 	Patient cannot walk Neuromuscular system works Sometimes visual aids compensate and override faulty brain processing of walking mechanism	Other apraxias Other frontal lobe signs	Normal pressure hydrocephalus Frontal lobe disease



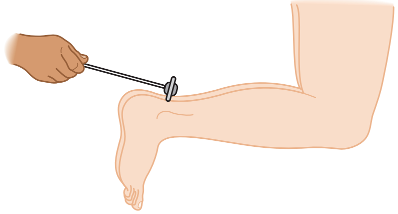
Eliciting the knee reflex L3, 4 – strike the quadriceps and watch it contract and the knee extend



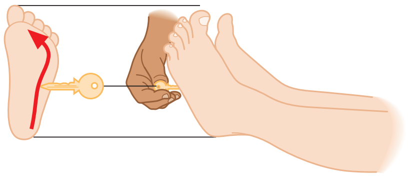
Reinforcement may be used to enhance reflexes which are difficult to elicit (ask patient to clasp hands tightly as shown or clench teeth)



Eliciting the ankle reflex of recumbent patient (*Bend your knee slightly and let it flop to the side*) L5, S1 (mostly S1) – strike the Achilles tendon, having induced relaxed tone in the calf muscle by adjusting the amount of ankle flexion and watch for plantar flexion and calf contraction



Alternative method is to strike the sole of the foot to stimulate sudden Achilles stretch



Plantar response – scrape the outer border of the foot from heel to toe and then across sole of the forefoot. Watch the toes curl (normal) or extend (positive Babinski's sign – upper motor neuron lesion, or withdrawal)

Alternative stimuli include stimulating the lateral aspect of the foot (Chaddock's sign) or running the thumb and index finger down the medial aspect of the tibia (Oppenheim's reflex) – both stimuli only of use if present

Figure 3.48 Lower limb reflexes.

SUMMARY BOX – GAIT EXAMINATION SEQUENCE

- Observe the patient walking.
- Note any obvious inward turning of foot or scissoring (*spastic*).
- Observe the patient turning and note any loss of arm swing (*Parkinsonian*); note posture.
- Observe the patient standing (and then walking) on their heels and toes (*high stepping/foot drop*).
- Observe patient walking heel to toe or 'tandem' walking (*cerebellar*).
- Check Romberg's test (*sensory ataxia*); this is only positive if the patient is more unsteady with eyes closed than open – 'pseudo-Rombergism' is common because, without vision, unsteadiness is always a little worse – and a truly positive Romberg's test is associated with proprioceptive and vibration sense impairment occurring in dorsal column disease and some peripheral neuropathies.
- Observe the patient squatting (*proximal myopathy*).

Cases

CASE 3.16 VISUAL FIELD DEFECTS

Instruction

Please examine this patient's eyes/visual fields and comment on your findings.

Recognition

There is (depending on the site of the lesion):

- A left/right *central scotoma*
- *Tunnel* (more correctly *funnel*) vision
- *Unilateral blindness*
- *Bitemporal hemianopia*
- *A left/right homonymous hemianopia*
- *A left/right homonymous quadrantanopia*
- *Loss of vision in the left/right eye with macular sparing.*

Interpretation

Confirm the diagnosis

What to do next depends upon the defect (Fig. 3.49).

What to do next – consider causes/assess other systems

Central scotoma

This indicates disease of the macula or nerve fibres from the optic nerve head (optic disc) that supply it. Look for evidence of disease at the macula or disc such as diabetic maculopathy or optic atrophy. Five signs of optic nerve damage are listed in Box 3.30.

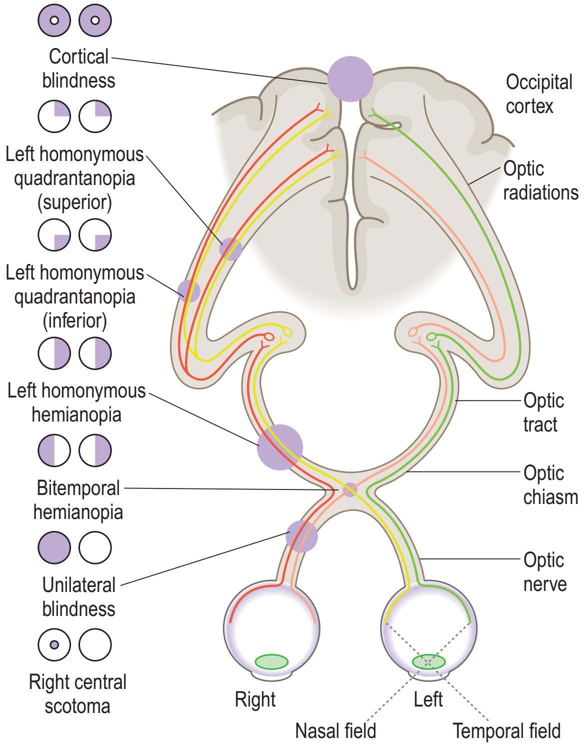

Cortical blindness
Left homonymous quadrantanopia (superior)
Left homonymous quadrantanopia (inferior)
Left homonymous hemianopia
Bitemporal hemianopia
Unilateral blindness
Right central scotoma
Occipital cortex
Optic radiations
Optic tract
Optic chiasm
Optic nerve
Right
Left
Nasal field
Temporal field

Figure 3.49 Visual field defects (visual field testing and visual field defects).

Box 3.30 **Five signs of optic nerve damage**

1. Central scotoma
2. Decreased visual acuity
3. Decreased colour vision
4. Relative afferent papillary defect (the most sensitive and specific sign)
5. Optic atrophy

Unilateral blindness

This indicates damage is to the eye itself.

Bitemporal hemianopia

This implies a lesion at the optic chiasm. A pituitary tumour may cause compression from below the optic chiasm. Look for signs of acromegaly (Fig. 3.50) or hypopituitarism. Rare causes include craniopharyngiomas, which compress the chiasm from above, meningiomas and aneurysms.

Homonymous hemianopia

This usually results from a total or partial anterior circulation stroke (TACS or PACS). A right TACS or PACS causes a left homonymous hemianopia – look then for a left supranuclear facial palsy and left upper motor neuron limb signs.

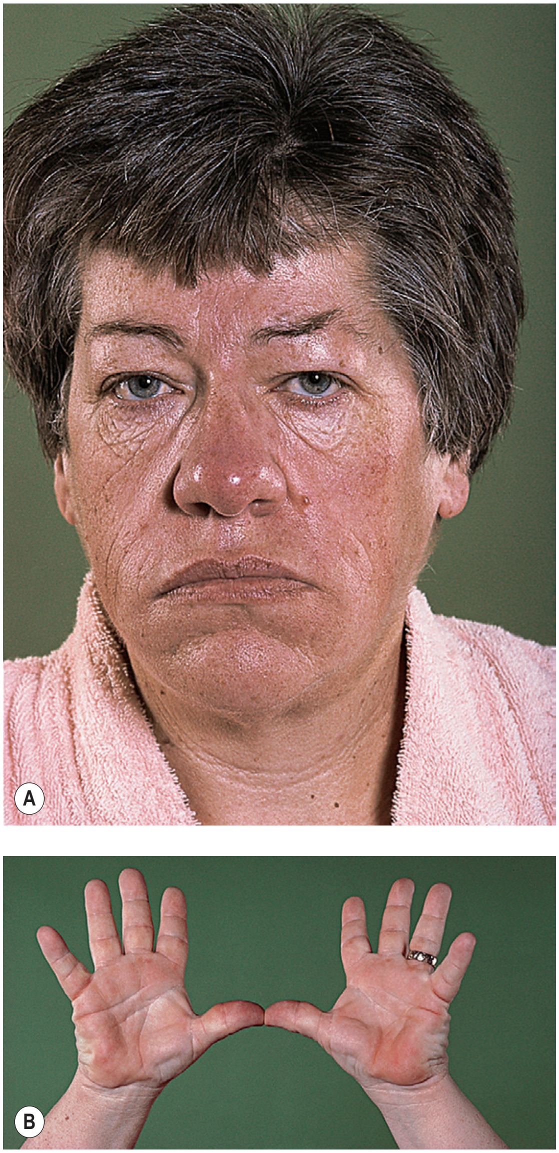


Figure 3.50 (A, B) Acromegaly.

Homonymous quadrantanopia

Consider a lesion in the temporal radiations if there is a superior homonymous hemianopia and in the parietal radiations if there is an inferior homonymous quadrantanopia. The cause again is usually a contralateral TACS or PACS. Quadrantanopias also arise from occipital lobe disease.

Cortical blindness

This is due to bilateral posterior cerebral artery strokes. The macula is spared because the macular cortex is supplied by the middle cerebral artery. Structural lesions destroying a hemioccipital cortex can cause complete contralateral blindness and visual hallucinations.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis. A visual field defect that is part of a TACS or PACS might lead to a discussion about stroke (Case 3.27).

Consider function

Comment on the functional significance of visual loss.

Discussion

List some causes of a visual field defect in one eye

- Scotoma
- Altitudinal defect (lesion confined to the upper or lower half of the visual field but crossing the vertical meridian) – usually a retinal artery branch problem
- Funnel vision (e.g. retinitis pigmentosa)

CASE 3.17 OCULAR NERVE LESIONS

Instruction

Please examine this patient's eyes / eye movements and discuss your findings.

Recognition

Third-nerve (oculomotor) palsy

The left / right eye adopts a '*down and out*' position because only the superior oblique and lateral rectus muscles are intact (Fig. 3.51). There is *ptosis* and the *pupil is dilated* if there is parasympathetic damage. Because the parasympathetic nerves destined for the pupillary sphincter are entwined around the third nerve, compressive lesions damage them whilst intrinsic (medical) causes such as diabetes spare them. Medical causes tend to be painless.

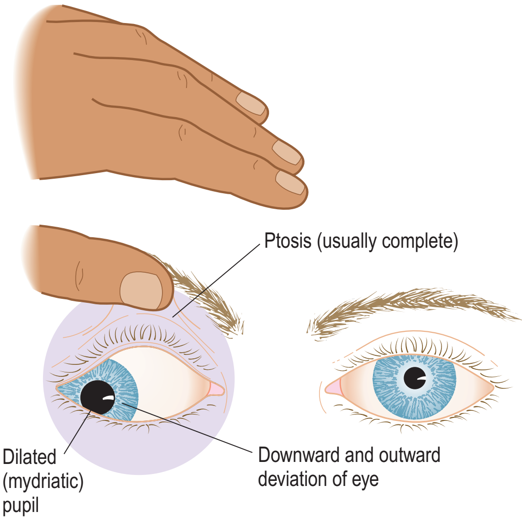

Ptosis (usually complete)
Dilated (mydriatic) pupil
Downward and outward deviation of eye

Figure 3.51 Right third-nerve palsy – neutral gaze.

Sixth-nerve (abducens) palsy

There is a gaze palsy, the left / right eye *failing to abduct* (Fig. 3.52).

Fourth-nerve (trochlear) palsy

Isolated fourth-nerve palsies are rare. Unopposed external rotation of the affected eye may result in a compensatory head tilt.

Interpretation

Confirm the diagnosis

The type of ocular palsy is usually clear if a single lesion is present. If this is not the case, consider the possibility of a complex ophthalmoplegia.

What to do next – consider causes

Tell the examiners possible sites of lesions, as follows.

Brainstem

The lesion may be of the nerve or of its nucleus connecting with central pathways. Causes include vascular lesions (isolated sixth-nerve palsies often with diabetes), demyelination and compressive lesions. Look for diabetic retinopathy and tell the examiners you would exclude diabetes.

Basal area

Causes include infection (bacterial, fungal or tuberculous infection), carcinomatous meningitis, basal infiltration from neurosarcoid or lymphoma, or infiltration from the nasopharynx or sinuses.

- Multiple lower cranial nerves are often involved, with a bulbar palsy.
- A posterior communicating artery aneurysm may compress the third nerve and is often painful.
- The third nerve may occasionally be stretched by a prolapsing temporal lobe (haemorrhage) and the sixth nerve may be stretched over the petrous tip by posterior fossa tumours. These ocular palsies are 'false localising' signs.

Cavernous sinus and orbit

Sepsis, tumours, intracavernous carotid aneurysms and infiltrative conditions such as Wegener's granulomatosis may damage ocular nerves as they traverse the cavernous sinus.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis.

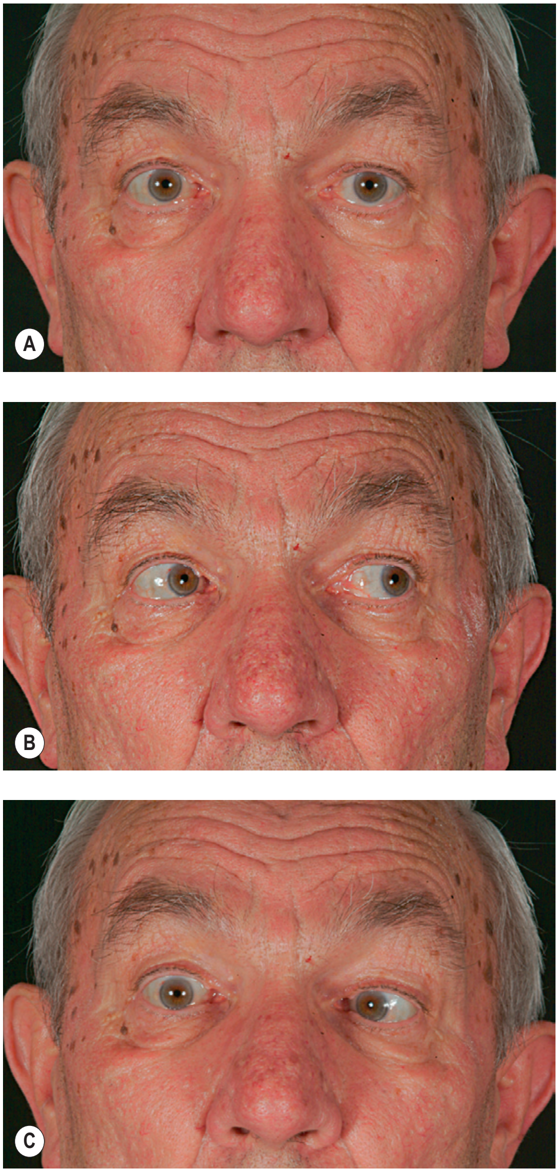


Figure 3.52 Right sixth-nerve palsy: (A) primary position, (B) looking left, (C) looking right.

Consider function

Comment on the functional significance of diplopia.

Discussion

What are the actions of the muscles controlling eye movements?

These are shown in Figure 3.53. The rectus muscles are straightforward. The medial rectus of one eye and the lateral rectus of the other work as a conjugate pair for horizontal conjugate gaze. The actions of the obliques are more difficult to remember:

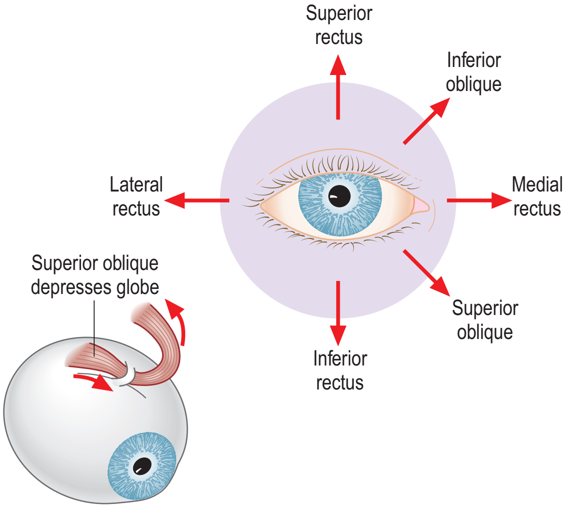


Figure 3.53 Actions of the muscles controlling eye movements (insert: action of superior oblique).

- When abducting, the superior and inferior rectus muscles dominate vertical gaze.
- When adducting, the superior and inferior oblique muscles dominate vertical gaze.
- Superior oblique, unlike superior rectus, depresses the eye whilst inferior oblique, unlike inferior rectus, elevates the eye! This is because the oblique muscles swing through hooks of tissue then double back on the globe to exert traction on it in a line of pull contrary to their nomenclature (Fig. 3.53 insert).
- As the oblique muscles sit slightly medially, they also attempt rotatory movements of the eyes, being unsuccessful in normal circumstances because of the opposing strength of other muscles. Acting alone, superior oblique would cause internal rotation or ‘intorsion’, and inferior oblique external rotation or ‘extorsion’.

By which ocular nerves are these muscles supplied?

- Oculomotor nerve – superior oblique, inferior rectus, medial rectus and inferior oblique
- Abducens nerve – lateral rectus
- Trochlear nerve – superior oblique

How does ophthalmoplegia cause diplopia?

When you take a romantic walk with your partner on a sunny day you may catch the sunlight in her or his eyes and see that it falls on exactly the same spot on each eye. Likewise, images from the world around us fall on corresponding spots of each retina. Slight displacement of either eye causes diplopia or double vision.

Which is the false image in diplopia?

The direction of gaze in which separation of images and corresponding diplopia is maximal is the direction of action of the paretic muscle. The false image (resulting from the paretic eye) falls progressively away from the macula and is always the outer or peripheral image seen. By covering the paretic eye this false image disappears.

What is meant by the term dysconjugate gaze?

This simply means that the eyes do not move together synchronously.

What is meant by the term strabismus or squint?

Strabismus or squint refers to misalignment – convergence (exotropia) or divergence (esotropia) – in the primary position (looking straight ahead), which remains constant in all directions of gaze. Cranial nerve ocular palsies and lateral and vertical gaze palsies arising from supranuclear disturbances should not be termed 'squints'.

What is meant by the term latent strabismus?

The visual axes are misaligned, even in the primary or neutral position, due to an imbalance of muscle tone rather than paresis. We all have a tendency to this, overcome by fusion mechanisms. It manifests in those with a history of a childhood squint, especially when tired. The squint does not settle in either eye. Rather, it is an angle that remains fixed between the eyes in any direction of gaze.

How might a latent strabismus be confirmed?

The cover test may be useful in eliciting a latent squint. To elicit the squint a hand covers one eye. The covered eye moves towards the squinting position, whilst the free eye fixes on an object. When the covered eye is uncovered, the squint is transiently observed.

Is ophthalmoplegia always due to a cranial nerve lesion?

No. It can arise from cranial nerve, neuromuscular junction or muscle abnormalities. Myasthenia gravis causes a complex ophthalmoplegia (multiple nerve lesions) and ptosis, and may be bilateral. A complex ophthalmopathy may also occur in thyroid eye disease owing to compression from orbital infiltration or thyrotoxic myopathy, and vasculitis. Rare ocular myopathies include some mitochondrial cytopathies and oculopharyngeal muscular dystrophy.

CASE 3.18 INTERNUCLEAR OPHTHALMOPLEGIA

Instruction

Pleases examine this patient's eye movements and proceed as you think appropriate before discussing your findings.

Recognition

On horizontal gaze, the abducting eye appears impatient because the *adducting eye is slow*. There is *divergent gaze* and the *abducting eye* appears to be coaxing the slow adducting eye, saying to it 'come on, come on!' in the only way it knows – with coarse, jerky *nystagmus* (Fig. 3.54)!

Interpretation

Confirm the diagnosis

This combination of eye anomalies is specific to internuclear ophthalmoplegia. Be alert, however, to the possibility of bilateral internuclear ophthalmoplegia.

What to do next – consider causes

In internuclear ophthalmoplegia the medial longitudinal fasciculus is damaged, most commonly by demyelination in multiple sclerosis. Look for signs of optic nerve damage – central scotoma, decreased visual acuity, decreased colour vision, relative afferent pupillary defect and optic atrophy – and tell the examiners you would look for other signs of demyelination, e.g. cerebellar signs, spastic paraparesis, sensory disturbance or bladder catheterisation.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis, usually the severity of multiple sclerosis.

Consider function

Comment on the functional significance of diplopia.

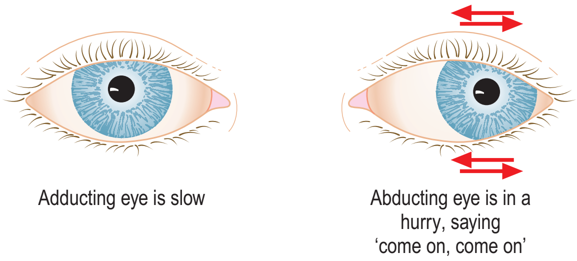

Adducting eye is slow
Abducting eye is in a hurry, saying 'come on, come on'

Figure 3.54 Internuclear ophthalmoplegia.

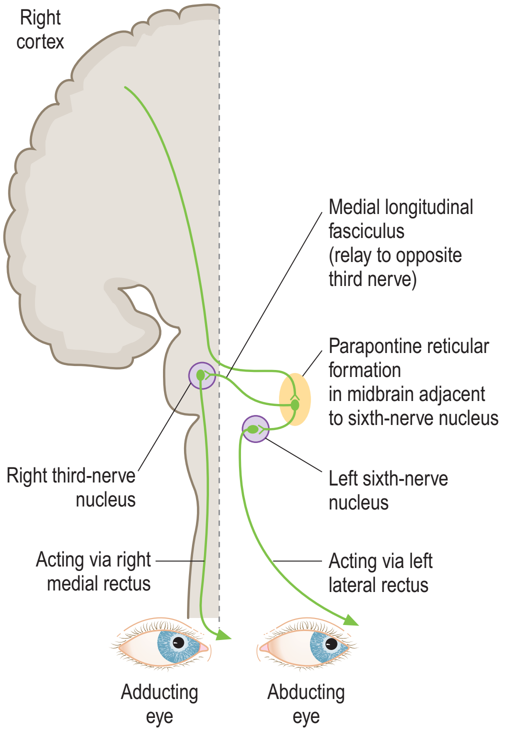

Right cortex
Medial longitudinal fasciculus (relay to opposite third nerve)
Parapontine reticular formation in midbrain adjacent to sixth-nerve nucleus
Right third-nerve nucleus
Left sixth-nerve nucleus
Acting via right medial rectus
Acting via left lateral rectus
Adducting eye
Abducting eye

Figure 3.55 The role of the medial longitudinal fasciculus in voluntary gaze, looking to the left.

Discussion

Explain the mechanism of horizontal voluntary conjugate gaze and therefore how internuclear ophthalmoplegia arises

The supranuclear or central processes governing eye movements are not well established but the following are thought true:

- Saccadic movements, under voluntary control, are initiated in the frontal cortex.
- Pursuit movements are initiated in the parieto-occipital cortex.
- The eyes must continuously adjust in relation to the position of the head in space, and this requires complex vestibular and proprioceptive inputs mediated through the brainstem.
- The eyes must move together, requiring synchronous contraction of ocular muscles in one eye and reciprocal muscles in the other. Monkeys relied on this evolution of binocular vision to judge swinging distances and evade death!
- Vertical gaze is mediated by the midbrain and not well understood. Skew deviation refers to eyes misaligned at different vertical levels.

Box 3.31 Horizontal voluntary gaze and how internuclear ophthalmoplegia (INO) arises

Higher initiating pathways descend from the frontal cortex to the level of the contralateral sixth-nerve nucleus at the parapontine reticular formation (PPRF). Some neurons from the PPRF stimulate the adjacent sixth-nerve nucleus. Other neurons from the PPRF travel back upwards and decussate to stimulate the opposite third-nerve nucleus via a pathway called the medial longitudinal fasciculus (MLF) (Fig. 3.55). The MLF allows the lateral rectus of one eye and the medial rectus of the other to contract synchronously. Each cerebral hemisphere controls horizontal gaze in the contralateral direction. The right hemisphere stimulates the ipsilateral third nerve and the contralateral sixth nerve and the eyes look to the left.

Damage to the MLF causes INO. Bilateral INO (BINO) is common because of the close midline proximity of the right and left MLF.

- Horizontal gaze is mediated by the pons and the best understood horizontal gaze mechanism is that of voluntary gaze (Box 3.31).
- The role of the medial longitudinal fasciculus in voluntary gaze is illustrated in Figure 3.55.

CASE 3.19 NYSTAGMUS

Instruction

Please examine this patient's eyes/eye movements and discuss your findings.

Recognition

There is difficulty in maintaining conjugate deviation. The *abducting eye drifts slowly back to the central position* (slow, pathological phase) and *then flicks back to its correct position* (fast phase). The direction of nystagmus, by convention, is the direction of the fast phase. This is known as *jerk nystagmus*.

Interpretation

Confirm the diagnosis

Nystagmus refers to involuntary eye movements. It begins as a slow pursuit movement followed by a fast, rapid resetting phase and is named by the direction of the fast phase. It may thus be right beating, left beating (collectively horizontal), up-beating, down-beating (collectively vertical), rotational, or direction changing. Jerk nystagmus should be distinguished from two other types of nystagmus:

■ **Physiological gaze-evoked nystagmus (also known as optokinetic, physiological or endpoint nystagmus).** This can be observed in normal individuals with gaze beyond 20° from straight ahead; this happens, for example, to a passenger in a car continuously watching the

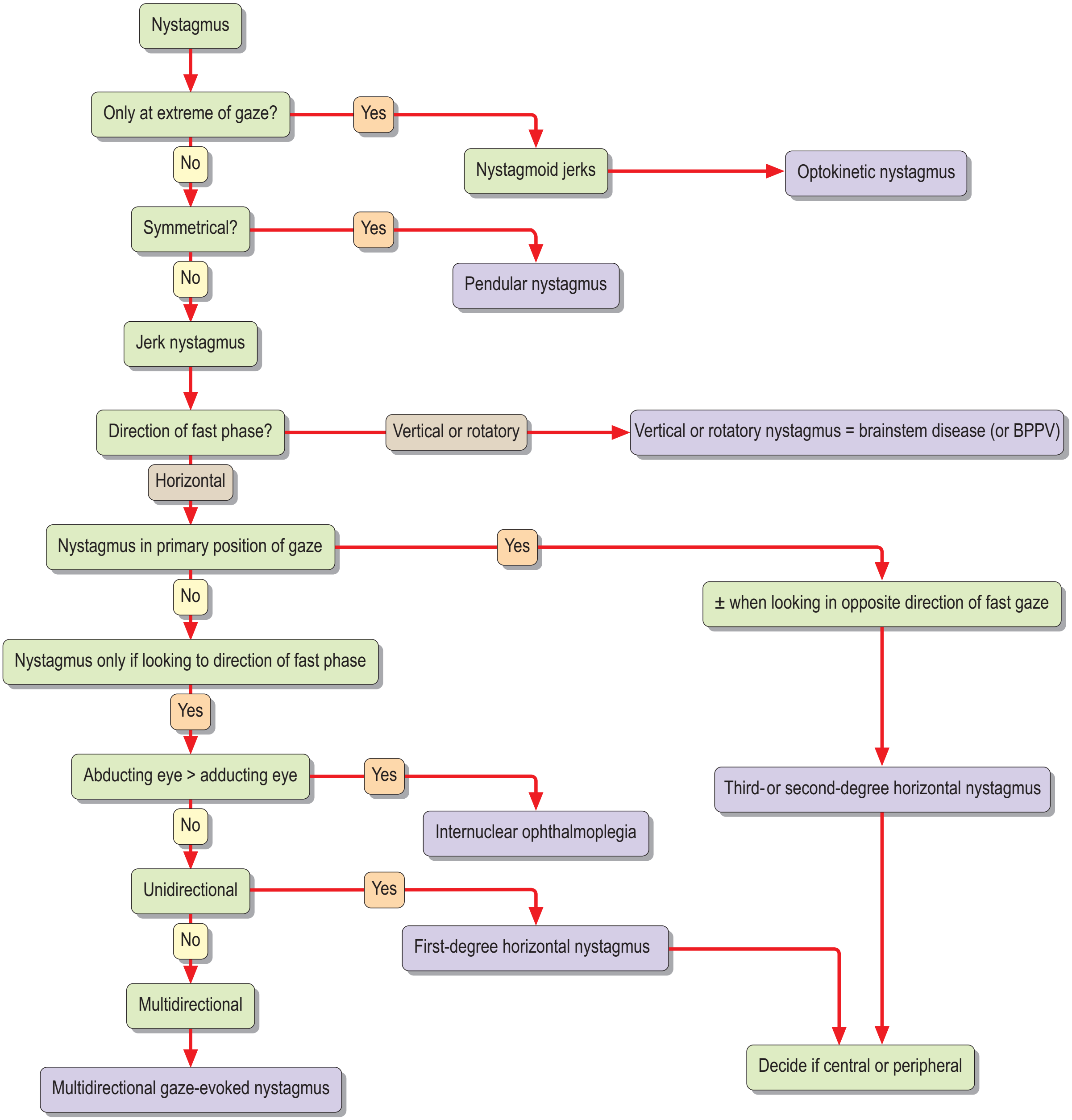

Nystagmus
Only at extreme of gaze?
Yes
Nystagmoid jerks
Optokinetic nystagmus
No
Symmetrical?
Yes
Pendular nystagmus
No
Jerk nystagmus
Direction of fast phase?
Vertical or rotatory
Vertical or rotatory nystagmus = brainstem disease (or BPPV)
Horizontal
Nystagmus in primary position of gaze
Yes
± when looking in opposite direction of fast gaze
No
Nystagmus only if looking to direction of fast phase
Yes
Abducting eye > adducting eye
Yes
Internuclear ophthalmoplegia
Third-or second-degree horizontal nystagmus
No
Unidirectional
Yes
First-degree horizontal nystagmus
No
Multidirectional
Decide if central or peripheral
Multidirectional gaze-evoked nystagmus

Figure 3.56 Causes of nystagmus. BPPV, benign positional paroxysmal vertigo.

world go by. Gaze-evoked nystagmus at gaze deviations of 20° or less is usually significant (e.g. cerebellar pathology). Physiological nystagmus is not associated with other eye movement abnormalities, whereas pathological gaze-evoked nystagmus is associated with other eye-movement abnormalities such as impaired smooth pursuit, vestibular–ocular reflex suppression and saccadic dysmetria.

■ **Pendular nystagmus.** This is a congenital difficulty with fixation, due to, for example, retinal disease; nystagmus is pendular or symmetrical with no distinct slow and fast phases, the speed and amplitude being equal in all directions, and the eyes seem to be searching forever for an elusive resting place.

What to do next – consider causes / assess other systems

Nystagmus may be caused by central or peripheral (vestibular) disease (Table 3.33). The mechanism of

Table 3.33 Central and peripheral nystagmus

	Central	Peripheral
Causes	Brainstem or cerebellar disease, e.g. ischaemia, space-occupying lesion, demyelination	Disease of the vestibular system
Type and direction of nystagmus	Often horizontal; may be vertical or multidirectional Jerk towards side of lesion in cerebellar disease	Spontaneous unidirectional nystagmus Jerk towards side of lesion (see head impulse test – Case 5.49 Vertigo)
Associated symptoms	Other neurological symptoms	Vestibular symptoms (vertigo)
Nausea and vomiting	Uncommon	Common
Effect of lying still	Does not improve symptoms	Improves symptoms
Recovery	Slow or no recovery	Recovers more quickly (central adaptation)

nystagmus is poorly understood but generally horizontal nystagmus may occur in a range of disorders affecting the cerebellum or brainstem and vertical nystagmus, much less common, is often attributed to midbrain pathology. If movements are not purely horizontal or vertical, they may be rotational (Fig. 3.56). This is almost always due to benign positional paroxysmal vertigo (BPPV) (Case 5.49 Vertigo). In practice, the cerebellum and its brainstem connections are intimately associated and the pathophysiology of these abnormal eye movements also involves brainstem nuclei. With progressive disease abnormal eye movements may also include: ocular dysmetria, an overshoot of target-directed fast eye 'saccadic' movements resembling limb past pointing and in which the eyes take a few moments to stabilise in the primary position after lateral gaze; ocular flutter, in which involuntary horizontal eye movements may occur in the primary position; and opsoclonus, in which the eyes continuously oscillate in all directions.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis.

Consider function

Comment on the functional significance of nystagmus.

Discussion

What do you know about nystagmus in the setting of vertigo?

Vertigo (Case 5.49) is caused by a problem with the vestibular system, and so may be caused by peripheral vestibular disease or disease of the vestibular connections in the brainstem. Central nystagmus may therefore occur in combination with vertigo if there is brainstem disease but without vertigo if there is pure cerebellar disease as brainstem vestibular connections will be preserved. Nystagmus may occur in some peripheral causes of vertigo, notably BPPV, where it is rotational.

CASE 3.20 PTOSIS

Instruction

Please examine this patient's eyes and discuss your findings.

Recognition

There is a *ptosis* (drooping upper eyelid) (Fig. 3.57).

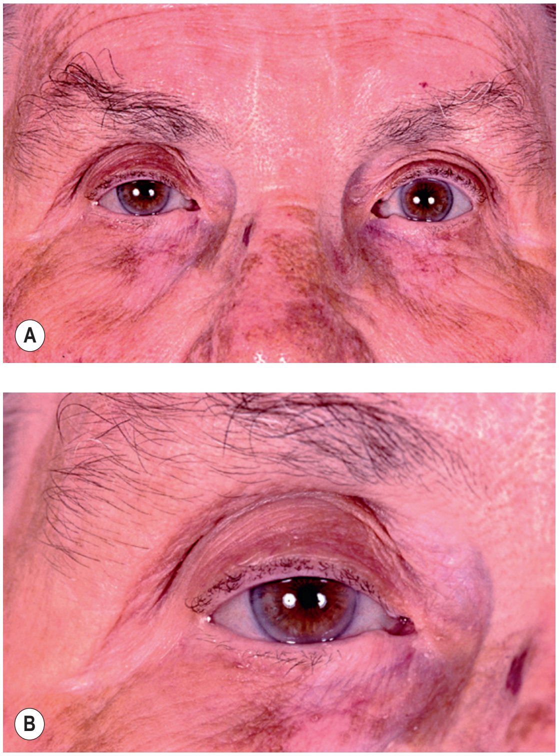


Figure 3.57 Ptosis (due to Horner's syndrome). (A) Face; (B) close-up of the eye.

Interpretation

Confirm the diagnosis

Ensure that the ptosis is not part of wider facial weakness.

What to do next – consider causes

Determine three things when you recognise ptosis (Box 3.32):

Third-nerve palsy

There is a dilated pupil on the side of the ptosis and a 'down and out' eye. Ptosis is usually complete (the levator palpabrae of the upper lid is third-nerve parasympathetically driven), so you may need to retract the lid to see these signs. The degree of ptosis alone should alert you to a third-nerve palsy.

Horner's syndrome

There is a small pupil on the side of the ptosis. Ptosis is partial (one small muscle component of the upper eyelid is sympathetically driven). Proceed as for Horner's syndrome (Case 3.23).

Myasthenia gravis

The pupils are normal. There is often a complex ophthalmoplegia and fatigable weakness of eyelid closure (seventh nerve) and eyelid opening (third nerve). Ptosis may be unilateral or bilateral.

Myotonic dystrophy

Pupils and eye movements are normal. Cataracts may be present. Ptosis is bilateral. The face is typically myotonic (Case 3.50).

Other

Rarer causes, with normal pupils and eye movements, include congenital ptosis, oculopharyngeal muscular dystrophy and oedema.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis. A Horner's syndrome due to an apical lung tumour, for example, has a vastly different prognosis from a third-nerve palsy in diabetes or myasthenia gravis.

Consider function

Comment on the functional significance of ptosis if it obscures the pupil; this is common in a third-nerve palsy.

Box 3.32 **Determine three things when you recognise ptosis**

1. Check for equal pupils.
2. Check eye movements.
3. Note whether the ptosis is unilateral or bilateral.

Discussion

What other causes of large / small pupils do you know of?

These are discussed in Cases 3.21 and 3.22.

CASE 3.21 LARGE PUPIL

Instruction

Please examine this patient's pupils and eyes and discuss your findings.

Recognition

There may be difficulty in deciding whether one pupil is *too big* or if the other is too small. Fortunately, knowledge of causes helps you to determine the abnormality.

Interpretation

Confirm the diagnosis

This most straightforward way is to consider causes.

What to do next – consider causes

Third-nerve palsy

Look for ptosis on the side of the larger pupil and a 'down and out' eye. Examine eye movements.

Holmes–Adie (tonic) pupil

This is likely to be due to damage to the ciliary ganglion. It often affects young women. The dilated pupil may be present long before attention is drawn to it. Holmes–Adie pupils are often widely dilated, and react slowly to light but react to accommodation. They are usually unilateral, at least at first. Check ankle and knee reflexes. Absent reflexes suggest Holmes–Adie syndrome. Holmes–Adie pupil is illustrated in Figure 3.58.

Traumatic iridoplegia

This is due to damage to the ciliary pupilloconstrictor mechanism.

Drug causes

If both pupils are dilated, consider a drug-induced cause. If both eyes are blind for any reason in which light is prevented from reaching both optic nerves and triggering the light reflex response, there will also be bilateral mydriasis.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis. A third-nerve palsy has many causes including stroke; a Holmes–Adie pupil is not a threat.

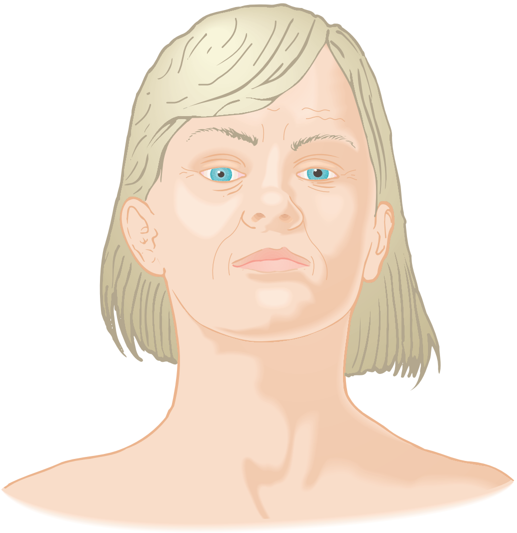


Figure 3.58 Holmes–Adie pupil.

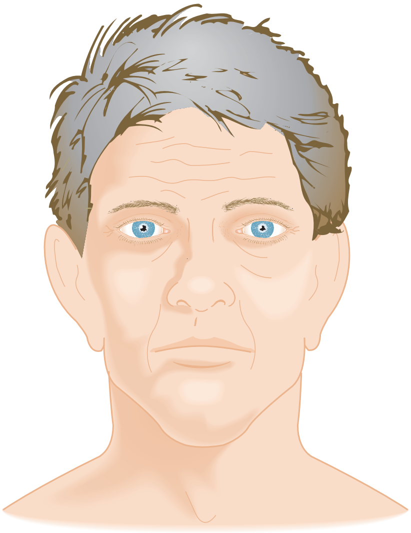


Figure 3.59 Argyll Robertson pupils.

Consider function

Comment on the functional significance of any visual loss or diplopia.

Discussion

List some drugs which act as mydriatics

- Tropicamide
- Cocaine or amphetamines
- Atropine and other anticholinergics (gardeners may develop mydriasis after contact with plants which have anticholinergic properties, 'cause–effect' often elusive without a thorough history)

What governs pupil size?

Pupil size is balanced by the effect on the ciliary muscle of constricting parasympathetic fibres acting via the ciliary ganglion and dilating sympathetic fibres acting via the superior cervical ganglion.

CASE 3.22 SMALL PUPIL

Instruction

Please examine this patient's pupils and eyes and discuss your findings.

Recognition

There may be difficulty in deciding if one pupil is *too small* or the other too big. *If there are no obvious signs of a third-nerve palsy* and the *larger pupil reacts quickly to light*, consider the causes of a small pupil.

Interpretation

Confirm the diagnosis

The most straightforward way is to consider causes.

What to do next – consider causes

Horner's syndrome

A Horner's syndrome is usually unilateral and the pupil reacts to light. Look for partial ptosis.

Argyll Robertson pupils

These are bilaterally small, irregularly shaped pupils that accommodate but do not react to light (Fig. 3.59). The accommodation reflex is subserved by more pupilloconstrictor fibres than the light reflex, and this may explain the dissociation. Argyll Robertson pupils are classically attributed to neurosyphilis.

Anisocoria

Twenty per cent of people normally have pupil asymmetry.

Age-related miosis

Both pupils can become smaller with age, but still react to light and accommodation, and this probably represents autonomic degeneration.

Consider severity / decompensation / complications

This relates very much to the underlying diagnosis. A Horner's syndrome may be due to an apical lung tumour, for example.

Consider function

Comment on the functional significance of any visual symptoms.

Discussion

List some common drugs causing miosis

- Pilocarpine
- Opiates

What causes of miosis might you consider in a patient with a depressed conscious level?

Opiates and pontine lesions such as haemorrhage or encephalitis cause miosis.

What cause of miosis would you consider were the eye red and painful?

- Iritis

CASE 3.23 HORNER'S SYNDROME

Instruction

Please examine this patient's pupils and anything else you think appropriate, and then discuss your findings.

Recognition (Fig. 3.60)

This is a syndrome with four potential features:

1. There is *miosis* (reduced pupillodilator activity) ipsilateral to the site of the lesion.
2. There is *partial ptosis* (because the levator palpebrae of the upper lid is partially supplied by the sympathetic nervous system as well as the parasympathetic supply that travels with the third nerve) ipsilateral to the site of the lesion.
3. There may be *anhidrosis* or absence of sweating (in preganglionic lesions only because the sweat gland outflow is proximal to the superior cervical ganglion).

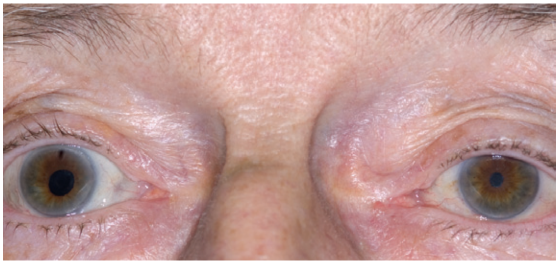


Figure 3.60 Horner's syndrome.

4. Apparent *enophthalmos* (because of paralysis of the upper and lower eyelid tarsus muscles) is seldom seen.

Interpretation

Confirm the diagnosis

Unlike a third-nerve palsy, ptosis is partial and the pupil is small (Fig. 3.60).

What to do next – consider causes

Horner's syndrome is the result of an interruption of the sympathetic chain and may originate anywhere along this chain. Lesions can occur within one of three general sites (Fig. 3.61).

The first neuron

The sympathetic pathway starts in the hypothalamus and travels through the brainstem, terminating in the grey matter of the spinal cord at C8–T1. Lesions include:

- Brainstem strokes, e.g. lateral medullary syndrome
- Demyelination in the brainstem or spinal cord
- Syringomyelia / syringobulbia, resulting in a 'cape' distribution of dissociated sensory loss
- Spinal cord tumours or trauma.

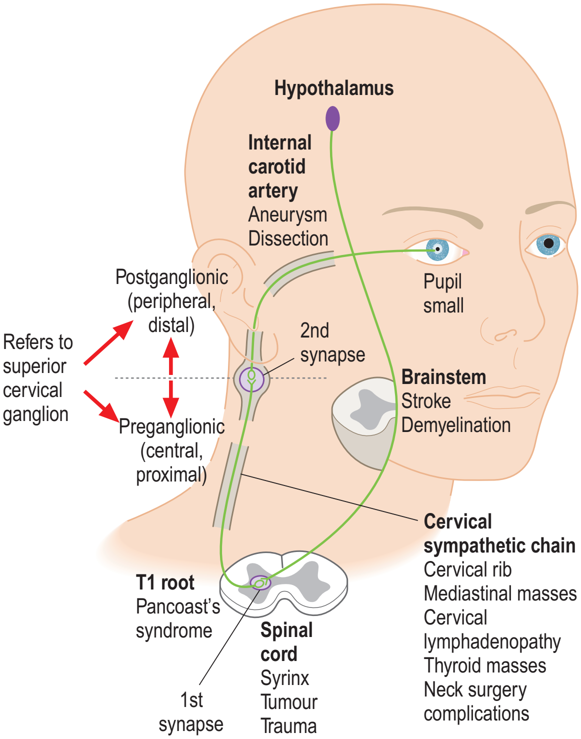

Hypothalamus
Internal carotid artery
Aneurysm
Dissection
Postganglionic (peripheral, distal)
Pupil small
Refers to superior cervical ganglion
2nd synapse
Brainstem
Stroke
Demyelination
Preganglionic (central, proximal)
Cervical sympathetic chain
Cervical rib
Mediastinal masses
Cervical lymphadenopathy
Thyroid masses
Neck surgery complications
T1 root
Pancoast's syndrome
Spinal cord
Syrinx
Tumour
Trauma
1st synapse

Figure 3.61 Horner's syndrome.

The second neuron

Sometimes referred to as the preganglionic neuron, in reference to the superior cervical ganglion (SCG), the sympathetic pathway travels from C8 to T1 via their nerve roots to the SCG. Preganglionic (also known as central or proximal) lesions are the most common causes of Horner's syndrome and include:

- Pancoast's syndrome, in which a tumour of the thoracic inlet infiltrates and causes pain in the distribution of T1 or C8; percuss and auscultate the supraclavicular area for signs of consolidation and look for ipsilateral wasting of the small muscles of the hand
- A cervical rib, which may be confirmed by chest X-ray and may cause thoracic outlet syndrome
- A mediastinal mass; look for signs of superior vena cava obstruction
- Cervical lymphadenopathy
- Thyroid masses
- Complications of neck surgery.

The third neuron

The postganglionic sympathetic pathway travels from the SCG in close proximity to the carotid artery and innervates the pupil (via long ciliary nerves which traverse around the eye), the blood vessels of the eye (via vasomotor fibres in the nasociliary branch of the trigeminal nerve) and the upper and lower lid tarsus muscles (which open the eye and oppose the action of orbicularis). Postganglionic (otherwise known as peripheral or distal) lesions include carotid aneurysms and carotid dissection.

Consider severity / decompensation / complications

Tell the examiners that a Pancoast's tumour implies invasive disease.

Consider function

This depends on the underlying cause.

Discussion

How might you determine the site of a Horner's syndrome lesion?

This is usually by identifying the cause. The use of chemical eye drops to determine if a lesion is central or peripheral is historical.

Can loss of pain and temperature sensation occur in Horner's syndrome?

The sympathetic pathway in the brainstem lies close to the spinothalamic tracts and contralateral body loss of pain and temperature sensation is frequent in Horner's syndrome arising from the brainstem.

What is thoracic outlet syndrome?

This is impingement of the subclavian arteries, which may occur with cervical ribs but which is often a variation of normal anatomy and dependent upon position (patients may experience paraesthesia and arterial symptoms in the arms on elevating the arms).

CASE 3.24 CEREBELLOPONTINE ANGLE SYNDROME

Instruction

Please examine this patient's cranial nerves and then discuss your findings.

Recognition

Any combination of *cranial neuropathies* involving the *trigeminal*, *facial* and *vestibulocochlear* nerve may occur. *Corneal reflex* loss is often the first sign, followed by facial sensory loss. Facial weakness can be a late sign. There may be *nystagmus*. There may be *sensorineural hearing loss*.

Interpretation

Confirm the diagnosis

A combination of pontine emanating cranial neuropathies without other neurological findings should alert you to this diagnosis. In practice, cerebellar signs and long tract involvement may occur depending upon the exact site of the lesion and the cause.

What to do next – consider causes

Cerebellopontine angle lesions, including acoustic neuromas and meningiomas, may cause slowly progressive hearing loss or tinnitus. Vertigo may occur. The next step is neuroimaging.

Consider severity / decompensation / complications

Tumours causing this syndrome are often benign but very awkwardly situated.

Consider function

Tell the examiners that hearing loss may be the first difficulty for patients.

Discussion

What is the cerebellopontine angle?

This is a triangle between the cerebellum, lateral pons and petrous bone (Fig. 3.62). Cranial nerves V–VIII emerge into it from the pons in craniocaudal sequence. The

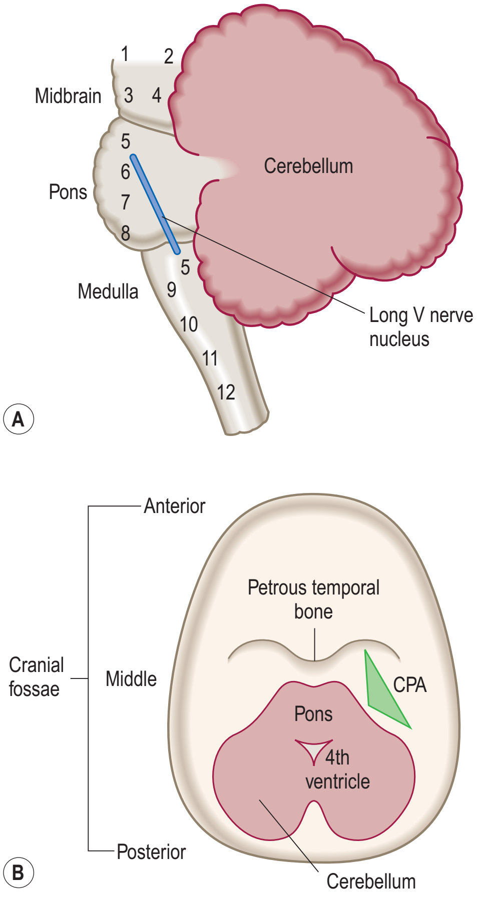


Figure 3.62 The cerebellopontine angle (CPA).

cerebellopontine angle stops just above IX, which emerges from the medulla.

What are the functions of the trigeminal nerve?

The trigeminal nerve divides into three from the trigeminal ganglion, which lies on the petrous tip. Each division conveys sensation (from many distal branches) from the face.

Ophthalmic

This runs via the superior orbital fissure and cavernous sinus conveying sensation from the forehead and scalp. The nasociliary branch supplies the nostril and the tip and upper border of the nose, carries sympathetic fibres to the pupil and conveys the sensory limb of the corneal reflex.

Maxillary

This runs via the inferior orbital fissure and cavernous sinus conveying sensation from the cheek, much of the oral cavity and midface. One branch thickens into a special ganglion called the pterygopalatine ganglion. This receives preganglionic parasympathetic fibres from the nervus intermedius (a branch of the facial nerve), which supply the lacrimal gland.

Mandibular

This exits at the foramen ovale and supplies the jaw and lower face. It also carries motor branches to the muscles of mastication, the masseter, which is very strong (jaw closure), and the pterygoids, which are weak (jaw opening). Alligators and crocodiles demonstrate how powerful masseters and weak pterygoids confer evolutionary advantage.

What trigeminal neuropathies do you know of?

Trigeminal neuropathies may be part of a wider cerebellopontine angle syndrome, with loss of the corneal reflex often the first clinical sign. Other clinical conditions affecting the trigeminal nerve include herpes zoster ophthalmicus and trigeminal neuralgia.

What is trigeminal neuralgia?

This is a rare but characteristic pain syndrome with sudden and severe lancing pain lasting from seconds to minutes within the trigeminal nerve distribution, typically the maxillary or mandibular branches, often evoked by trivial stimulation in 'trigger zones'. Atypical symptoms with altered sensation may occur. It is a variable condition, and some patients only have one episode.

Most cases are still referred to as idiopathic, although vascular compression of the trigeminal nerve by an aberrant loop of artery or vein at its exit site from the brainstem is increasingly appreciated. A minority of cases are the result of nerve compression by a tumour, or occur in multiple sclerosis. Accordingly, the threshold for magnetic resonance imaging that includes the brainstem should be low.

The differential diagnosis includes dental disease, temporomandibular joint pain, persistent idiopathic facial pain ('atypical facial pain'), migraine and temporal arteritis.

Treatment is usually effective. Carbamazepine is first-line treatment. Surgical treatments are possible if carbamazepine is ineffective or not tolerated. Ablative surgery is seldom associated with severe complications but may cause facial sensory loss and there is a high rate of pain recurrence; microvascular decompression has a lower relapse rate but a higher risk of serious complications.

What do you know about sensorineural hearing loss?

This is discussed in Case 5.49 (Vertigo and hearing loss).

What is jugular foramen syndrome?

The final four cranial nerves, IX, X, XI and XII, occupy an area around the jugular foramen. Lesions in this area may extend from the cerebellopontine angle, or arise as localised or diffuse basal skull lesions as in tuberculosis or meningeal malignancy. Lesions may provoke a bulbar palsy.

CASE 3.25 FACIAL NERVE PALSY

Instruction

Please examine this patient's face. Discuss your differential diagnosis.

Recognition

There is *paralysis of one side of the face* (Fig. 3.63). In the *upper face*, the *eye does not close fully* (the eyeball may roll up on attempted closure – Bell's phenomenon). Muscles that do not work include the orbicularis oculi (closes eye), the frontalis (raises eyebrow) and the corrugator superficialis (frowns). In the *lower face*, the *mouth droops* and the *nasolabial fold is smooth*.

Interpretation

Confirm the diagnosis

A facial nerve palsy is just that! There is paralysis of the upper and lower parts of the face because of a lesion in the facial nerve (Fig. 3.64). Candidates often talk of 'lower motor neuron facial nerve weakness'. By definition, facial nerve lesions are lower neuron lesions because the facial nerve is a cranial nerve innervating the face! Upper motor neuron facial weakness, due to a lesion in supranuclear neurons innervating the facial nerve, spares the upper face because there is bilateral supranuclear or upper motor neuron innervation selectively to those facial nerve fibres that supply the upper face. This said, bilateral innervation might not be even (e.g. 70 : 30 rather than 50 : 50), such that a little upper facial weakness may be seen.

What to do next – consider causes

Tell the examiners that you would consider whether loss of taste to the tongue with loss of salivation, hyperacusis or loss of lacrimation has occurred. These respectively, theoretically, help localise the lesion proximally (Fig. 3.64).

Knowing the possible causes of facial nerve palsy enables you to rapidly look for other relevant signs, as follows.

Bell's palsy

This is probably viral. Usually, but not always, the only sign is facial weakness, the presumed site of inflammation distal in the facial canal.

Ramsay Hunt syndrome

This is the result of reactivation of herpes zoster virus in the geniculate ganglion. Taste tends to be affected and there may be vesicles over the external auditory meatus. Occasionally vesicles hide exclusively within the ear canal.

Parotid swellings

Look and feel for a swollen parotid gland, which may be the result of infection secondary to a duct calculus, a parotid tumour or trauma to the area.

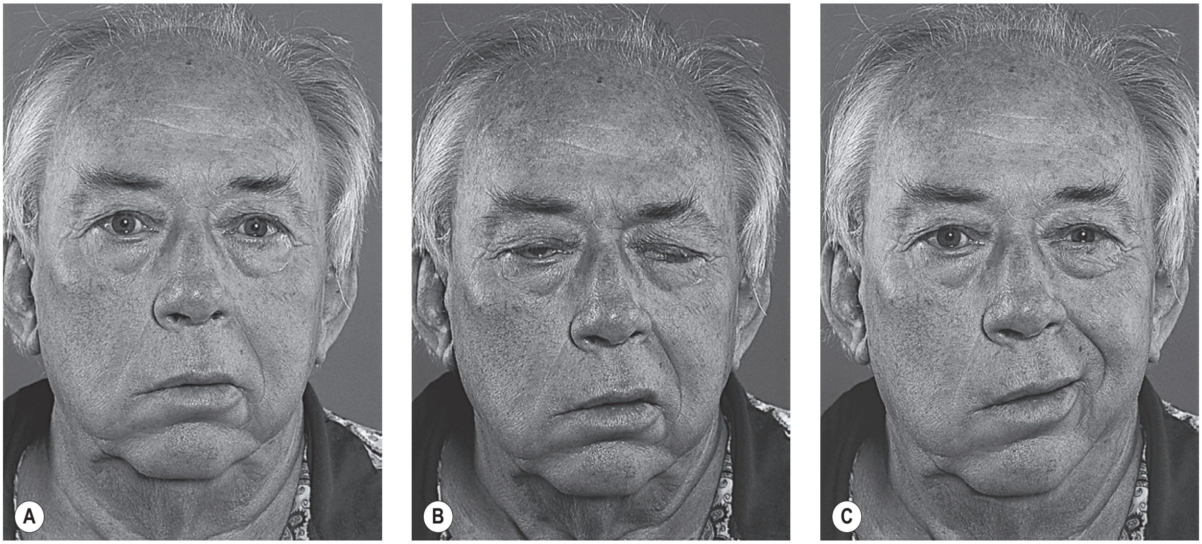
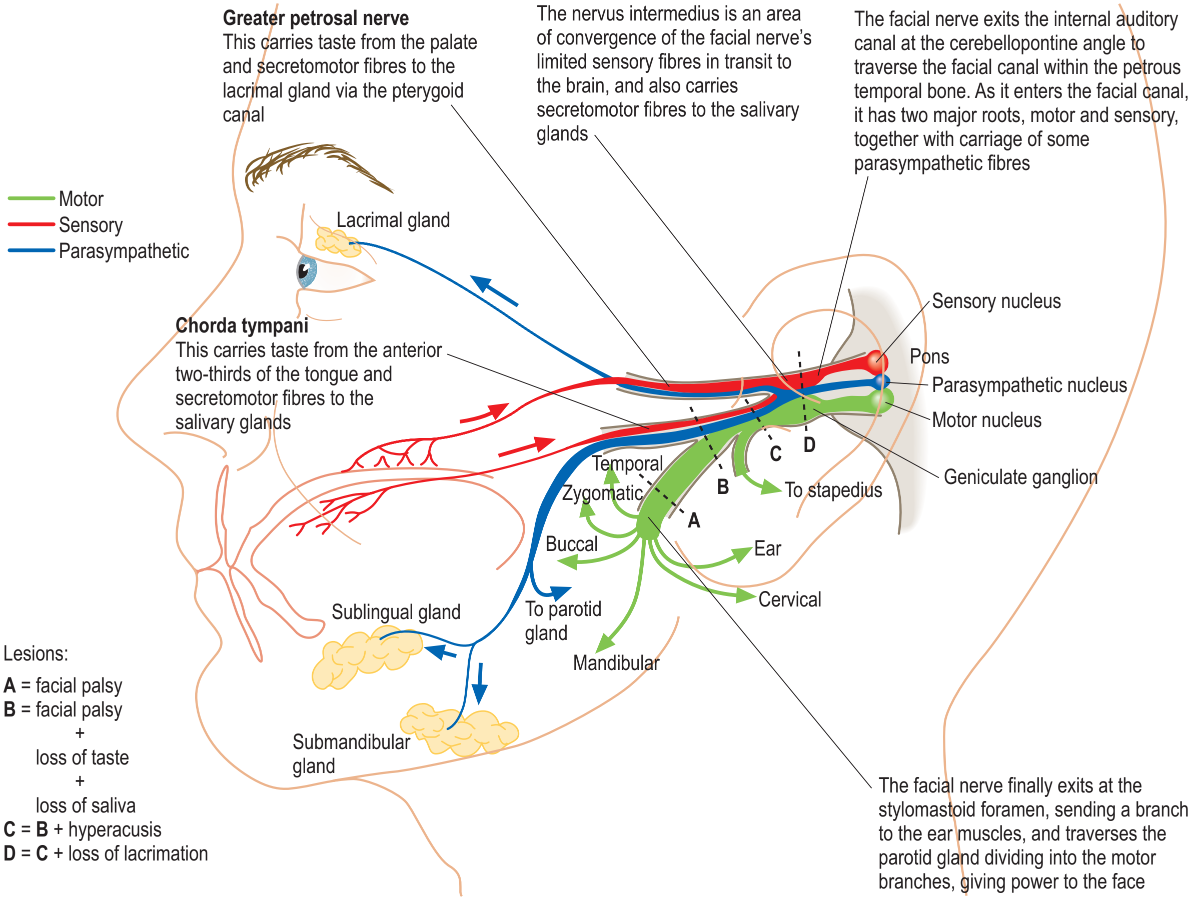


Figure 3.63 Facial nerve palsy: (A) at rest, (B) closing eyes, (C) smiling.



Greater petrosal nerve
This carries taste from the palate and secretomotor fibres to the lacrimal gland via the pterygoid canal

The nervus intermedius is an area of convergence of the facial nerve's limited sensory fibres in transit to the brain, and also carries secretomotor fibres to the salivary glands

The facial nerve exits the internal auditory canal at the cerebellopontine angle to traverse the facial canal within the petrous temporal bone. As it enters the facial canal, it has two major roots, motor and sensory, together with carriage of some parasympathetic fibres

Chorda tympani
This carries taste from the anterior two-thirds of the tongue and secretomotor fibres to the salivary glands

The facial nerve finally exits at the stylomastoid foramen, sending a branch to the ear muscles, and traverses the parotid gland dividing into the motor branches, giving power to the face

Motor
Sensory
Parasympathetic
Lacrimal gland
Sensory nucleus
Pons
Parasympathetic nucleus
Motor nucleus
Geniculate ganglion
C
D
B
A
Temporal
Zygomatic
To stapedius
Buccal
Ear
Cervical
To parotid gland
Mandibular
Sublingual gland
Submandibular gland
Lesions:
A = facial palsy
B = facial palsy
+
loss of taste
+
loss of saliva
C = **B** + hyperacusis
D = **C** + loss of lacrimation

Figure 3.64 The facial nerve and localisation of damage.

Brainstem strokes or demyelination

These may involve the facial nerve nucleus and precipitate facial weakness.

Cerebellopontine lesions

These should always be considered, especially if there is loss of the corneal reflex or hearing.

Cholesteatoma

This is a rare cause, in which epithelial cells accumulate behind the tympanic membrane, sometimes leading to perforation. An ear, nose and throat specialist appraisal is mandatory.

Other causes, often infective, sometimes causing bilateral facial nerve weakness

Causes include human immunodeficiency virus infection, Lyme disease, Guillain–Barré syndrome, neurosarcoid and bilateral Bell's palsy.

Consider severity / decompensation / complications

This very much relates to the underlying cause. Facial palsy as part of Guillain–Barré syndrome, for example, clearly has different implications from a Bell's palsy; the former might just as easily recover, but the condition is potentially much more serious. Most Bell's palsies will recover, but persistent weakness can occur.

Consider function

Tell the examiners you would wish to assess bulbar function. Tell the examiners you would wish to exclude exposure keratitis and consider corneal protection.

Discussion

Which viruses probably cause Bell's palsy?

Herpes simplex virus type 1 and herpes zoster virus are probably frequently to blame.

Would you treat Bell's palsy?

Combined treatment with oral aciclovir or valaciclovir or famciclovir for 7–10 days and prednisolone 60 mg reduced to zero over 3 weeks is recommended by some, although the evidence supporting antiviral treatment is inadequate and most would favour corticosteroid alone. Treatment of partial Bell's palsy is controversial but a few patients do not recover if left untreated. Treatment is probably most effective before 72 hours and less effective after 7 days.

What do you know about Lyme disease?

This is a spirochaetal disease, *Borrelia burgdorferii*, transmitted by ticks, originally identified in Lyme, Connecticut, in the 1970s and now highly prevalent in the UK, especially in the New Forest and on Exmoor and Dartmoor, where sheep rather than deer have become the main tick hosts. Acquisition by humans usually requires ticks being on the body for many hours. Incubation is between 1 and 2 weeks. Early localised disease may include erythema migrans, headaches and nausea. Early disseminated disease occurs after a few weeks and may include erythema migrans, facial nerve palsy, meningism, palpitations and polyarthritis. Late persistent disease evolves over a few months and may include cardiac conduction disturbances and vertigo. Chronic disease, over years, may include meningo-encephalitis, neuropsychiatric disease, myocarditis and arthritis.

CASE 3.26 BULBAR PALSY

Instruction

This woman has been in the intensive therapy unit recently. Please examine her speech.

Recognition

There is *dysarthria*. There is *nasal speech (nasal escape)*. Speech may have a 'drowning' or 'choking' quality and it often seems that 'everything is in the way'. There may be salivary pooling.

Interpretation

Confirm the diagnosis

Try to distinguish a bulbar from a pseudobulbar palsy although this is not always so easy in practice. A bulbar palsy due to unilateral cranial nerve insults should, in addition to the characteristic bulbar pattern of speech, produce:

- A uvula that is pulled away from side of unilateral weakness – tenth-nerve palsy (Fig. 3.65)
- A tongue that deviates to the side of the lesion – twelfth-nerve palsy (Fig. 3.66)

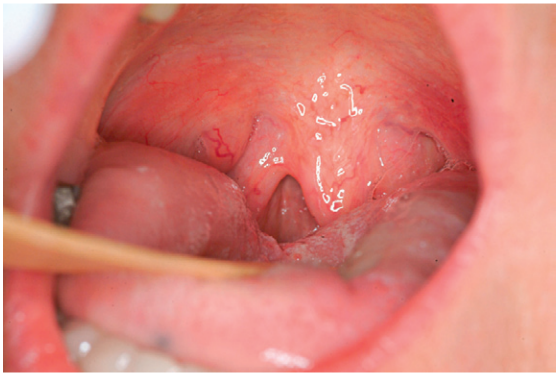


Figure 3.65 Bulbar palsy: tenth-nerve palsy – note asymmetric uvula.

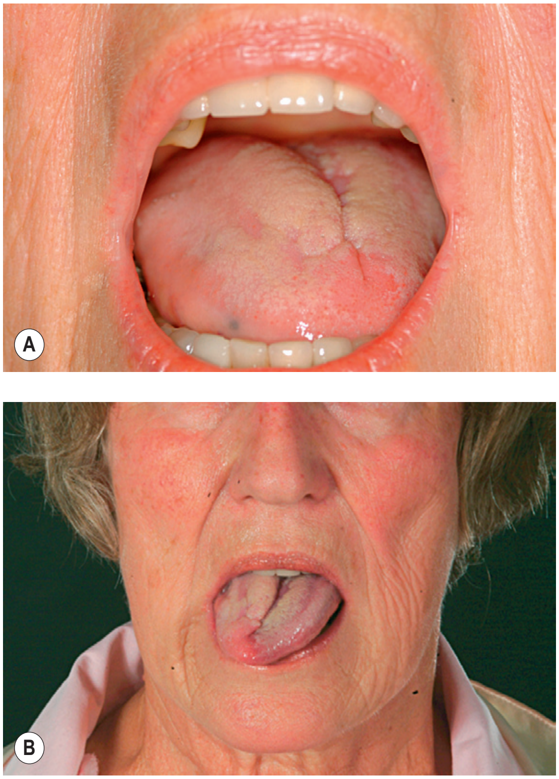


Figure 3.66 Bulbar palsy – twelfth-nerve palsy: (A) tongue at rest, (B) tongue protruded.

A bulbar palsy due to bilateral cranial nerve, neuromuscular or muscle disease may not produce asymmetry but the characteristic bulbar pattern of speech is present.

What to do next – consider causes / assess other symptoms

Causes of a bulbar palsy are listed in Box 3.33.

Box 3.33 Causes of a bulbar palsy

- Motor neurone disease
- Guillain–Barré syndrome
- Myasthenia gravis
- Lambert Guillain–Eaton myasthenic syndrome
- Basal meningitis
- Botulism (*Clostridium botulinum*)
- Tetanus
- Diphtheria
- Lyme disease
- Human immunodeficiency virus-related neuropathy
- Malignancy

Tell the examiners full assessment includes testing all cranial nerves, noting any ptosis and asking about diplopia (myasthenia), testing power, testing reflexes (Guillain–Barré syndrome) and checking for fatigability (myasthenia).

Consider severity / decompensation / complications

Tell the examiners that you would ask about nasal regurgitation of fluids or food particles with aspiration or attacks of choking and that you would wish to assess vital capacity (and ask about respiratory symptoms) and arrange a swallow assessment.

Consider function

Tell the examiners that you would ensure assessment by a speech and language therapist. Mention if there is a nasogastric tube or percutaneous gastrostomy tube *in situ*.

Discussion

Explain the difference between a bulbar palsy and a pseudobulbar palsy

This is explained in Box 3.25.

List some investigations you might consider for a patient with a rapidly progressive bulbar palsy

- Visualisation of the vocal cords by an ear, nose and throat specialist
- Brain / brainstem imaging
- Cerebrospinal fluid examination
- Tensilon (edrophonium) test / acetylcholine receptor antibodies
- Infection serology and testing for botulism, tetanus and diphtheria
- Human immunodeficiency virus testing

What would you regard as essential immediate management steps for a patient with a rapidly progressive bulbar palsy?

Assessment of respiratory rate and vital capacity and early liaison with the intensive therapy unit and a neurologist.

CASE 3.27 ANTERIOR CIRCULATION STROKE SYNDROMES

Instruction

Please examine this patient's speech, face and limbs and discuss your findings.

Recognition

Circulation and cortical representation

Circulation

Each lobe does not have a discrete blood supply and so *stroke syndromes* are different from *lobe syndromes*. It is helpful to briefly revise brain vascular anatomy (Fig. 3.67).

Cortical representation

In terms of stroke, it is useful to remember that each cortical hemisphere represents the contralateral limbs and cranial nerves (homunculus). The left hemisphere has a major role in language. The right hemisphere has a major role in awareness of the left side of the body. This said, both hemispheres contribute to language and awareness (Fig. 3.68).

Total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS) and posterior circulation stroke (POCS)

Bamford et al devised and published this classification in Oxford in 1991 and it is now widely used because it is relatively straightforward, widely applicable and prognostic (Fig. 3.69). The suffix stroke may be substituted for infarct (I) or haemorrhage (H).

Total anterior circulation stroke (TACS) (Fig. 3.69A,B)

The anterior communicating artery is a protective anastomosis between the two anterior cerebral arteries and so middle cerebral artery territory strokes are much more common. Strokes arising in the proximal trunk of the middle cerebral artery or the internal carotid artery result in a *total anterior circulation syndrome* (Box 3.34). TACS accounts for around 20% of strokes.

Cortical weakness often affects the face and arm more than the leg.

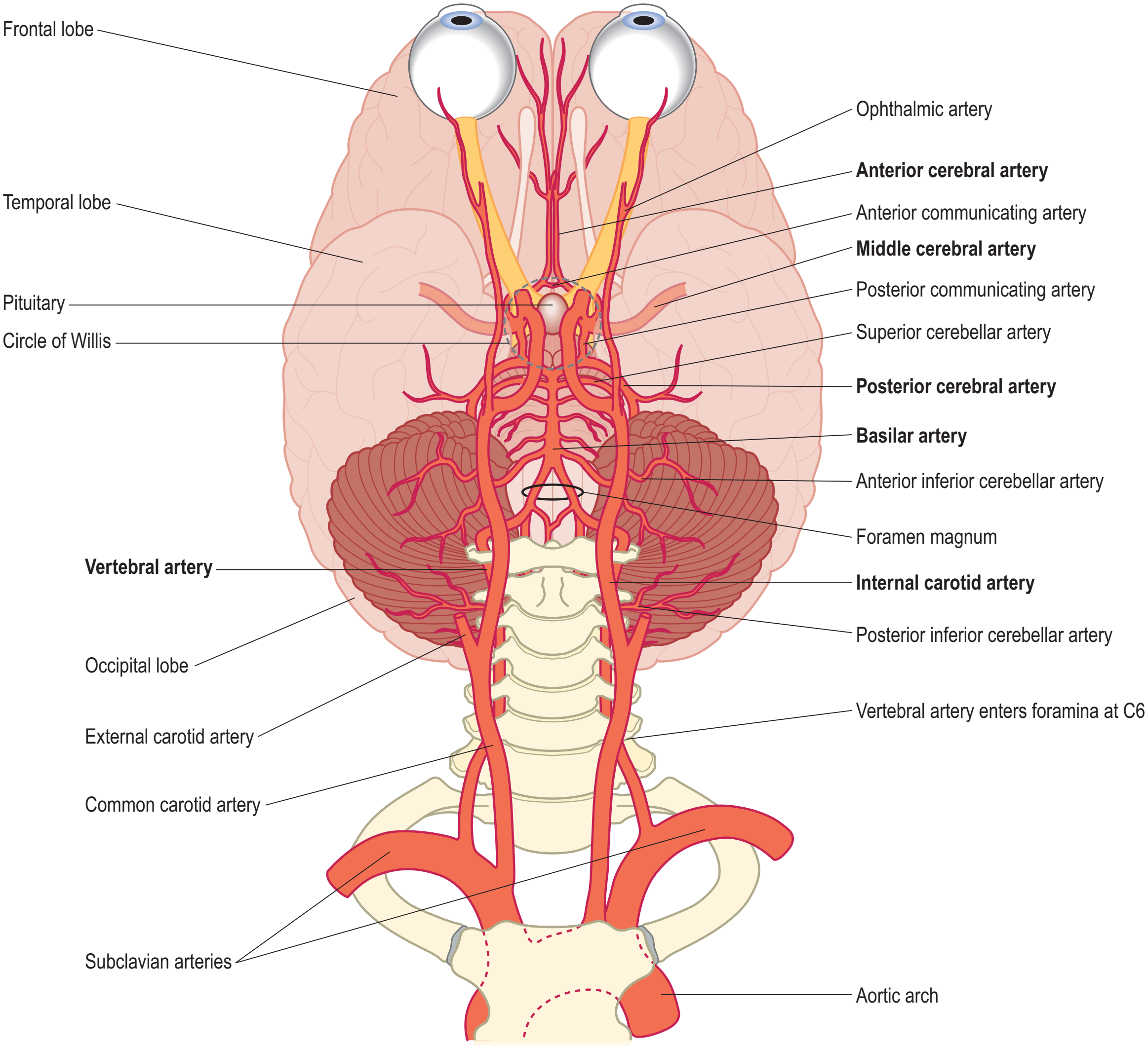

Frontal lobe
Temporal lobe
Pituitary
Circle of Willis
Ophthalmic artery
Anterior cerebral artery
Anterior communicating artery
Middle cerebral artery
Posterior communicating artery
Superior cerebellar artery
Posterior cerebral artery
Basilar artery
Anterior inferior cerebellar artery
Foramen magnum
Vertebral artery
Internal carotid artery
Posterior inferior cerebellar artery
Occipital lobe
External carotid artery
Vertebral artery enters foramina at C6
Common carotid artery
Subclavian arteries
Aortic arch

Figure 3.67 Blood supply to the anterior and posterior fossae. Patient looking up (artificially extending neck) to schematically show arrangement of blood vessels.

Bilateral vertebral arteries fuse to form a single midline basilar artery, these arteries collectively supplying the brainstem (medulla, pons and midbrain) and cerebellum. The basilar artery runs midline along the ventral surface of the brainstem, feeding it with small, deep perforators, and then merges with the circle of Willis, giving off the posterior cerebral arteries at the basilar bifurcation. The posterior cerebral arteries supply the upper brainstem, occipital lobes and visual cortex (via the terminal calcarine artery), posterior temporal lobes and thalamus (not visible here).

The anterior cerebral artery supplies the parasagittal cortex including the motor (predominantly frontal lobe) and sensory (predominantly parietal lobe) cortices for the leg. The middle cerebral artery supplies most of the lateral cortex, its main trunk dividing into three major branches; smaller lenticulostriate branches supply the anterior limb of the internal capsule and the basal ganglia. The main vessel terminates as a wisp in the occipital lobe supplying the macular cortex.

At the circle of Willis, note how the internal carotid artery essentially trifurcates into the middle cerebral artery, the anterior cerebral artery and the posterior communicating artery, the last providing communication with the posterior circulation via connection with the posterior cerebral artery; this connection is seldom sufficient to nourish the brainstem via the anterior circulation, however, in the event of basilar occlusion.

Note, too, that the anterior communicating artery provides some exchange of blood between the right and left anterior cerebral arteries; in the event of internal carotid artery occlusion, the middle cerebral artery is clearly compromised, and the anterior cerebral artery may or not be compromised depending upon the degree of compensation afforded by the anterior communicating artery. The anterior cerebral artery provides blood supply to leg fibres in the motor cortex, and so, in internal carotid artery occlusions, leg weakness may be a little more spared than arm and facial weakness, arm and face fibres in the motor cortex being much more fully dependent on middle cerebral artery supply; occlusion of the anterior cerebral artery distal to the anterior communicating artery could give rise to a leg monoparesis, and occluded branches of the middle cerebral artery similarly may produce restricted monoparesis of arm or paresis of face (partial anterior circulation strokes).

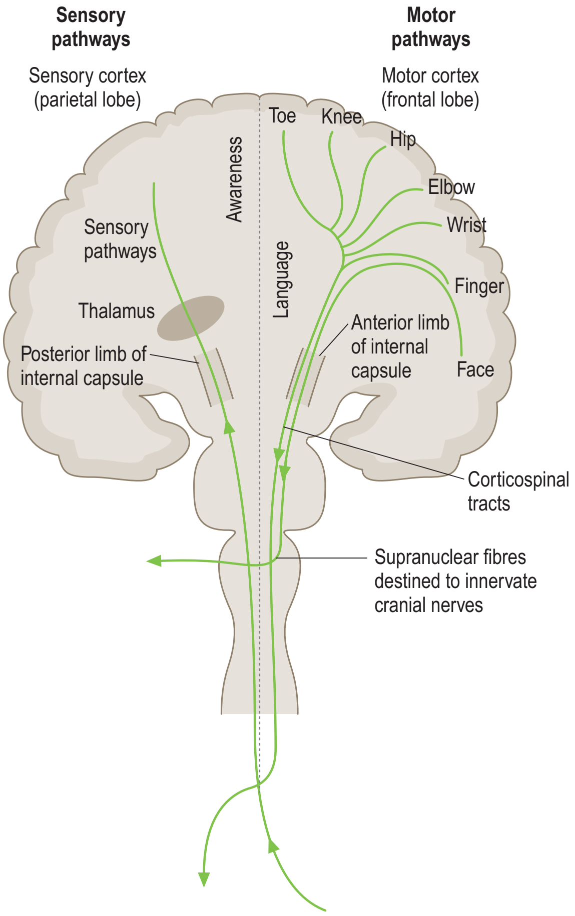

Sensory pathways
Motor pathways
Sensory cortex (parietal lobe)
Motor cortex (frontal lobe)
Toe
Knee
Hip
Elbow
Wrist
Finger
Face
Awareness
Language
Sensory pathways
Thalamus
Posterior limb of internal capsule
Anterior limb of internal capsule
Corticospinal tracts
Supranuclear fibres destined to innervate cranial nerves

Figure 3.68 Cortical representation of body structures.

Box 3.34 Total anterior circulation syndrome

This requires all three of:

- *Contralateral* hemiparesis or *weakness* of at least *two out of three of face, arm or leg*, usually with increased tone and reflexes, with or without contralateral hemisensory loss
- *Contralateral homonymous hemianopia* (infarcted optic radiations in parietal and temporal lobes)
- A higher cortical function abnormality, usually *dysphasia* if left total anterior circulation stroke (TACS) or *sensory inattention or neglect* if right TACS.

If a patient is drowsy or has a decreased Glasgow Coma Score and 1, then 2 and 3 are assumed.

In the first few hours after a stroke, some of the normally reliable upper motor neuron signs (spasticity, brisk reflexes, co-contraction, flexor or extensor spasms in response to noxious or proprioceptive stimuli) are immature or absent, making anatomical localisation difficult. Higher cortical deficits may be apparent, although sometimes only if vigilant to them, and include:

Box 3.35 Partial anterior circulation syndrome

This requires two out of the three total anterior circulation stroke criteria or restricted criteria:

- *Contralateral weakness of arm or leg or hand* or part thereof (corticospinal tract infarction referable to the appropriate area of homunculus) *or face* (supranuclear infarction of fibres supplying facial nerve). A monoparesis may be the sole manifestation of a partial anterior circulation stroke (PACS).
- Higher cortical dysfunction alone (*dysphasia or neglect*), which may be the only manifestation of a PACS.

Visual field defects are less common if the upper division of the middle cerebral artery is affected and motor and sensory deficits are uncommon if the lower division is affected.

- Dysphasia
- Apraxia (dominant, left parietal lobe often more so than right parietal lobe); for example, left frontal infarcts may cause right hemiparesis with apraxia of the hand
- Visual and sensory inattention or neglect (non-dominant, right parietal lobe often more so than left parietal lobe) or denial of disability (anosognosia)
- Visual agnosias (non-dominant parieto-occipital cortex)
- Alexia and agraphia (left angular gyrus).

Visual field defects are very helpful in anatomical localisation, particularly the superior and inferior quadrantinopias of temporal and parietal lobe lesions, respectively, and the hemianopia of an optic tract or occipital cortex lesion. Conjugate eye deviation (and sometimes head deviation), known as Prevost's sign, sometimes occurs in cortical strokes owing to disturbance in cortical or subcortical pathways involved in control of voluntary eye movements. Deviation is towards the side of the lesion. For example, in a right cortical stroke, disrupted signals to the left eye with normal signals to the right eye cause an imbalance in neural tone that causes the right eye to tend to move to the right at rest because of the absence of counter pull to the left; the left eye follows in a yoking manner because the pontine neural connections (e.g. the medial longitudinal fasciculus) to the left medial rectus are intact, leading to conjugate deviation of the eyes to the right.

Partial anterior circulation stroke (PACS) (Fig. 3.69C,D)

More common (around 35% of strokes) is a stroke arising in one of the middle cerebral artery's branches giving rise to a *partial anterior circulation syndrome* (Box 3.35).

Lacunar stroke (LACS) (Fig. 3.69E)

Small, localised infarcts are often the result of lipohyalinosis of penetrating arteries (lenticulostriate arteries) and are referred to as LACS (Box 3.36). They are very common, and often silent. They often affect the internal capsule; the anterior limb of the internal capsule relays only motor fibres and so strokes are pure motor whereas the posterior

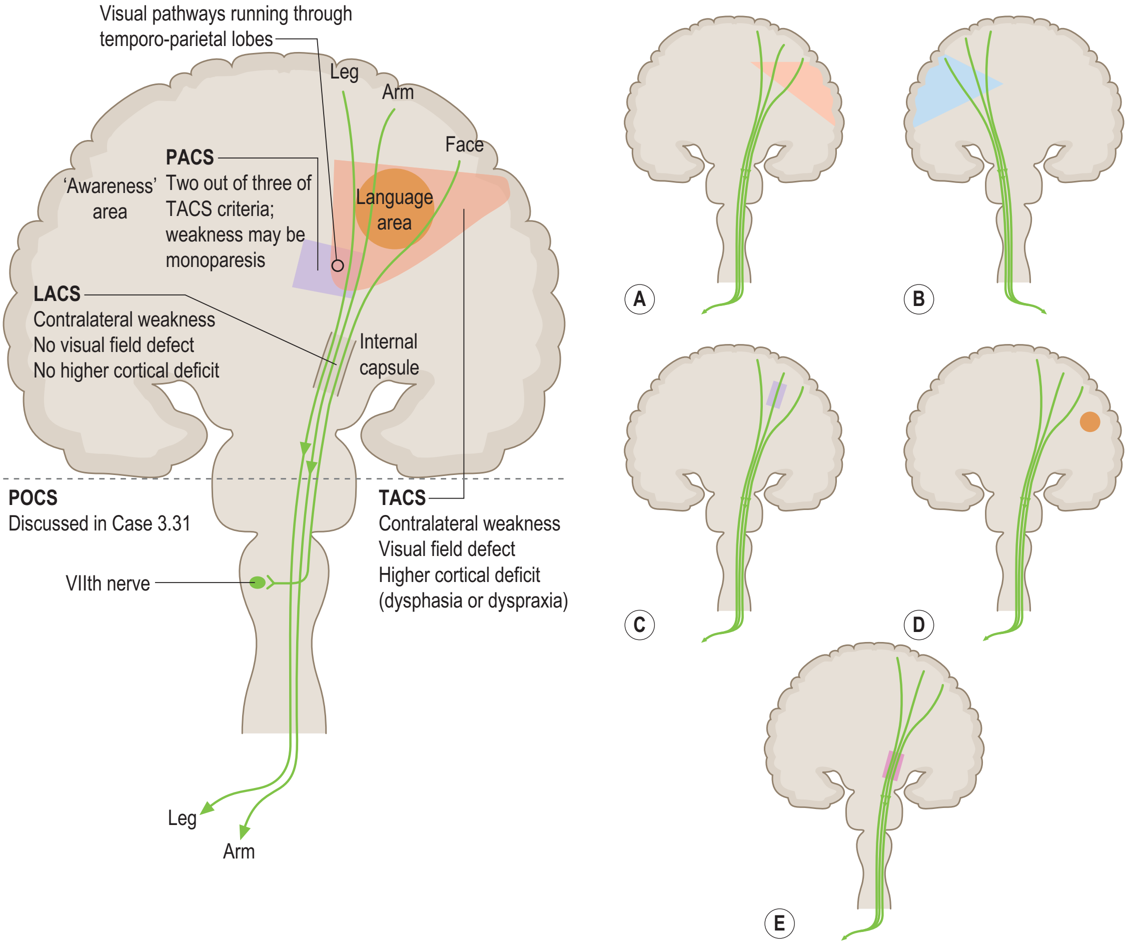

Visual pathways running through temporo-parietal lobes
Leg
Arm
Face
PACS
Two out of three of TACS criteria; weakness may be monoparesis
'Awareness' area
Language area
LACS
Contralateral weakness
No visual field defect
No higher cortical deficit
Internal capsule
POCS
Discussed in Case 3.31
TACS
Contralateral weakness
Visual field defect
Higher cortical deficit (dysphasia or dyspraxia)
VIIth nerve
Leg
Arm
A
B
C
D
E

Figure 3.69 Total or partial anterior circulation stroke (TACS, PACS), lacunar strokes (LACS) and posterior circulation stroke (POCS) (cerebellum not shown for simplification):
A Left TACS: right face, arm and leg weakness, right homonymous hemianopia, dysphasia.
B Right TACS: left face, arm and leg weakness, left homonymous hemianopia, neglect.
C Left PACS (in this case isolated to arm fibres): right arm weakness.
D Left PACS: dysphasia.
E Left pure motor LACS: right face, arm and leg weakness, +/– dysarthria, which may be a feature of a TACS, PACS or LACS (or POCS), often transient (see Box 3.37).

Box 3.36 **Lacunar stroke (LACS)**

This can affect the anterior or posterior circulation, but is most common in the basal ganglia and pons. Possible LACS is:

- Pure motor (contralateral arm, leg and facial weakness to a roughly similar extent, often with dysarthria)
- Pure sensory
- Sensorimotor
- Ataxic hemiparesis – contralateral hemiparesis and ipsilateral cerebellar signs due to small infarcts in the basal ganglia or pons.

There may be profound dysarthria owing to involvement of corticobulbar fibres, but the patient should not be dysphasic or have other cortical deficits.

limb of the internal capsule relays sensory fibres to the thalamus destined for the parietal lobe and strokes cause contralateral hemianaesthesia. LACS generally affects subcortical structures (e.g. basal ganglia, thalamus) and so does not exhibit higher cortical signs such as dysphasia or neglect. LACS occasionally stutters for a day or two as the occluding artery expands and contracts around its clot.

Strokes exemplify the eloquence of small parts of the brain, a minor fault evoking a clinical earthquake. The contemporary threat of atherosclerosis has taken evolution by surprise. As it is, the internal capsule, the main thoroughfare for nerve excursion from the cortex, has a disappointing blood supply ill-equipped for breakdown and an internal capsule LACS is a small area of damage with clinically large repercussions. The internal capsule is the motorway for all motor and sensory neurons whose distant homes were dotted in the widely spaced uplands of the homunculus. Those heading to work (the motor tracts) will never make it if the motor lanes of the internal capsule are closed. Those coming home from work (the sensory tracts) will never make it if the sensory lanes of the internal capsule are closed.

None of this is to say, of course, that LACS is more devastating than the higher cortical PACS or TACS. PACS or TACS tend to involve larger (middle cerebral) artery occlusions and so although the traffic is more widely dispersed above the internal capsule the damage is also on a larger scale. Conceivably, however, a small distal branch of the middle cerebral artery could be affected in isolation, damaging merely a few neurons' far upland homes on the map that is the homunculus; this might then give rise to weakness that is isolated to a small part of the limb, and may be mistaken for a peripheral nerve lesion, when in fact it is a small PACS, although in practice emboli tend to lodge themselves in vessels before reaching far upland streams.

Posterior circulation stroke (POCS) (see Fig. 3.69E)

POCS affects the brainstem, cerebellum and occipital lobes and is discussed in Case 3.31.

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about onset. Strokes are abrupt (or stepwise) clinically. They cause focal weakness. Strokes are thus primarily clinical diagnoses; infarcts are sometimes invisible on early scans and the role of imaging is to exclude stroke mimics and determine whether infarct or haemorrhage.

If facial weakness is a prominent sign, confirm it is an upper motor neuron or supranuclear facial weakness (Box 3.37; Fig. 3.70).

Tell the examiners you would arrange neuroimaging to confirm and characterise stroke and exclude stroke mimics.

What to do next – consider causes

Occlusive stroke

Strokes are usually occlusive (embolic or atherosclerotic with thrombosis). LACS is commonly a silent event seen on magnetic resonance imaging (MRI) as deep white matter changes. Atrial fibrillation is a very important stroke risk factor, more so for TACS and PACS than for LACS, as are valvular heart disease and cardiac thrombus, the latter notably after myocardial infarction. Carotid atherosclerosis is a major cause; this may be because of dislodged fatty atheromatous material or a mechanism the same as that in coronary syndromes in which a plaque may rupture, fissure or erode, triggering platelet aggregation and formation of thrombus, which leads to local occlusion or distal embolisation. Tell the examiners you would assess the risk factors. Most conventional risk factors – age, smoking, diabetes and obesity – are broadly similar for ischaemic stroke and heart disease but the continuous relationship between stroke and blood pressure is much steeper in stroke and plasma cholesterol concentration is less strongly associated in stroke. Less common causes of ischaemic stroke should always be considered (Table 3.34), and depression is a risk factor.

Haemorrhagic stroke

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) accounts for at least 10% of all strokes in the UK, and a greater proportion in some ethnic groups. It may present with a sudden focal neurological deficit or reduced consciousness. No clinical scoring system has been shown

Box 3.37 **Supranuclear control of facial and other cranial nerves**

All cranial nerves innervate the head, face and neck ipsilaterally. They receive innervation from supranuclear pathways via brainstem nuclei. Unfortunately, we cannot think of each cranial nerve as being innervated in the same way. Some are innervated only by a contralateral supranuclear pathway from the contralateral hemisphere, but some receive bilateral innervation, a supranuclear pathway from each hemisphere.

The supranuclear control of conjugate eye movements was discussed in Case 3.17.

The trigeminal motor nucleus receives bilateral supranuclear innervation. A unilateral supranuclear lesion does not therefore cause masticatory weakness.

The facial nerve's fibres supplying the upper face are bilaterally innervated from supranuclear pathways (Fig. 3.70). Fibres to the lower face only receive supranuclear innervation from the contralateral hemisphere. An upper motor neuron lesion therefore causes only contralateral lower facial weakness. It makes sense that we have evolved this way, the muscles for eye protection and chewing having a 'spare parachute'. However, there is much heterogeneity and, although some cranial nerve nuclei are bilaterally innervated, the contribution from each hemisphere is rarely 50 : 50. A patient with a left internal capsule stroke and right lower face weakness may also have subtle right upper facial weakness if the left hemisphere contributed more than 50% of supranuclear innervation to the right facial nerve.

If there is a spare parachute for chewing (trigeminal nerve) it makes sense to have one for swallowing. Supranuclear innervation to the nucleus ambiguus (the motor nucleus for the glossopharyngeal, vagus and accessory nerves) and the hypoglossal nerve, motor to tongue, is variable but bilateral in most people. The palate, vocal cords and tongue may be transiently weak after a stroke, but in many cases they recover quickly as compensation from the surviving hemisphere kicks in, and any residual speech difficulty is then the result of dysphasia rather than dysarthria. The exception is when bilateral lesions cause dysarthria with a pseudobulbar palsy. Supranuclear fibres controlling bulbar function are sometimes termed corticobulbar fibres.

The accessory nerve's supranuclear innervation is such that each hemisphere controls the ipsilateral sternomastoid and contralateral trapezius muscles. Contraction of both muscles enables the head to turn away from the hemisphere in question.

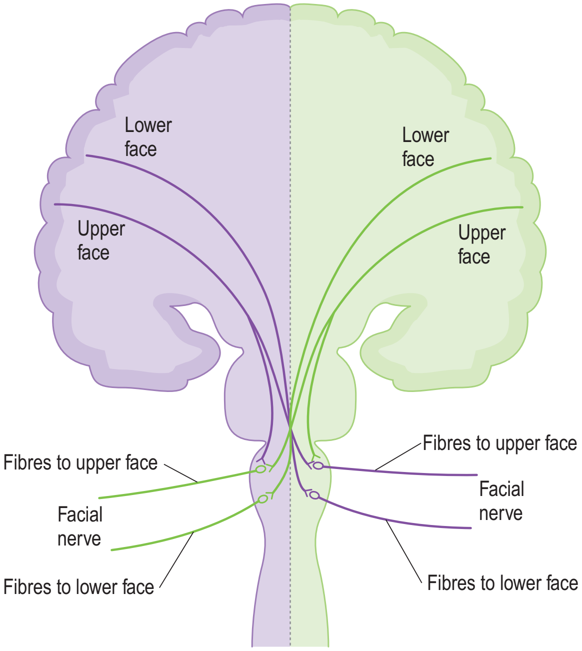


Figure 3.70 Supranuclear control of the facial nerve.

to reliably differentiate ICH from ischaemic stroke and timely imaging is key. The major risk factors for spontaneous ICH are systemic arterial hypertension, excess alcohol consumption, male sex, increasing age, and smoking, which may lead to secondary vascular changes such as small vessel disease and arterial aneurysms which may eventually cause ICH. Types of haemorrhagic stroke are outlined in Table 3.35.

Consider severity / decompensation / complications

TACS generally has a worse prognosis than PACS and PACS generally worse than LACS. POCS has generally a similar prognosis to LACS, but can be catastrophic depending upon the site.

Aspiration pneumonia is common in patients with speech and swallowing difficulties.

Consider function

Tell the examiners of the vital role of physiotherapists, occupational therapists and speech and language therapists in assessment and rehabilitation.

Discussion

What do you understand by the term stroke?

Symptoms of stroke include numbness, weakness or paralysis, slurred speech, blurred vision and severe headache. Stroke (World Health Organization definition) is a clinical syndrome of rapidly developing focal (or global as in subarachnoid haemorrhage) cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one. A transient ischaemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours. However, there are limitations to these definitions. For example, they do not include retinal symptoms (sudden onset of monocular visual loss), which should be considered as part of the definition of stroke and TIA. The symptoms of a TIA usually resolve within minutes or a few hours at most, and continuing neurological signs should be assumed to be due to a stroke and indeed more detailed imaging is revealing persistent damage in what would have formerly fitted the definition of a TIA. The term ‘brain attack’ is sometimes used to describe any neurovascular event. Around 140 000 strokes occur annually in the UK, with a 30–40% recurrence in the first year. Stroke is the third most common cause of death and the leading cause of disability.

What key advances in stroke care have been made in recent years?

Three major advances in stroke care are:

- The introduction of rapid access stroke/TIA clinics
- The increasing use of thrombolysis and the potential for invasive intervention
- The introduction of dedicated stroke rehabilitation units as well as acute stroke units, and the implementation of early supported discharge from hospital for selected patients.

How important are stroke units?

All people with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment, either from the community or from the emergency department. An acute stroke unit is a discrete area in the hospital staffed by a specialist stroke multidisciplinary team and has access to equipment for monitoring and rehabilitating patients. Regular multidisciplinary team meetings occur for goal setting. Stroke units save lives (number needed to treat (NNT) 33) and improve independence (NNT 20). They may be acute, rehabilitative or combined and evidence is that patients do much better than on mixed rehabilitation wards and undifferentiated medical wards. Mobile stroke units appear not to be as effective, and it seems that the combined beneficial features of a dedicated stroke unit cannot be reproduced outside it.

Does headache occur in strokes?

Headache is under-recognised. It is most common in haemorrhagic stroke, but occurs in around one-quarter of ischaemic strokes, in descending order of likelihood, in TIAs, thrombotic infarcts, embolic infarcts and lacunar infarcts. Artery territories giving rise to headache in descending order of likelihood are posterior cerebral, vertebral, basilar, middle cerebral and anterior cerebral. The

Table 3.34 Less common causes of ischaemic stroke that should be considered

Cause	Clue	Investigation	Treatment
Carotid or vertebral artery dissection	Can occur after trivial trauma A 'design fault' close to where the vertebral artery enters the vertebral foramina and skull results in vertebral artery kinking, exacerbated by neck movements and cervical spondylosis	Not always detected by magnetic resonance angiography, and conventional angiography may be necessary	Dissected endothelium provides a prothrombotic milieu. The question of antiplatelet versus anticoagulation therapy is unresolved Dissection itself usually resolves spontaneously
Cerebral vasculitis	Raised inflammatory markers	Autoimmune screen	Immunosuppression Treat cause
Giant cell arteritis	Headache	Erythrocyte sedimentation rate or C-reactive protein Temporal artery biopsy	High-dose corticosteroids
Bacterial endocarditis	Risk factors and signs	Raised inflammatory markers Blood cultures	Antimicrobial therapy
Thrombophilic disorders	Index of suspicion, e.g. young patient	Thrombophilia screen	Consideration of anticoagulation, but stroke in antiphospholipid syndrome is managed as for people without antiphospholipid syndrome
Migraine	Headache Acephalgic fortification spectra	Clinical diagnosis of exclusion	
Patent foramen ovale	Index of suspicion, e.g. young patient (but now known to be a cause of 'cryptogenic' stroke in all ages, especially if patent foramen ovale associated with atrial septal aneurysm)	Specialised echocardiography	Surgery
Fibromuscular dysplasia	Often younger females, often with renovascular hypertension, with other arteries involved (internal carotid)	Arteriography shows string of beads appearance	Surgery sometimes
Genetic syndromes, e.g. Fabry's disease	Family history	Genetic testing	Enzyme replacement or genetic treatment

cause is unclear but it may relate to altered vascular tone or release of vasoactive substances. Although headache is common in ischaemic stroke, particularly in posterior circulation large artery events, with or without dissection, severe headache raises concern about alternative diagnoses. Vague symptoms such as slurred speech, transiently blurred vision, unsteadiness, dizziness and clumsiness are anatomically unhelpful but do not exclude a focal ischaemic event.

List some stroke mimics

In order of frequency, these include:

- Seizure (far more likely than stroke if there is a history of epilepsy)
- Delirium
- Flare-up of old stroke (under-recognised but not uncommon in new illness and logical because exact symptoms and signs of a previous stroke in that territory are unlikely to be replicated)
- Syncope (global rather than focal event but surprisingly common mistake)
- Tumour (contrary to traditional teaching, may present acutely – just as strokes can occasionally disobey the acute rule)
- Psychiatric disturbance
- Alcohol- or drug-related symptoms.

Hypoglycaemia should always be excluded with acute neurological signs. Migraine should always be considered where there is episodic focal neurology.

Discuss the role of brain imaging in acute stroke

Imaging has hitherto used computed tomography (CT) to rapidly exclude ICH and detect certain stroke mimics. CT is readily available and thus allows the exclusion of contraindications to thrombolysis, and practical, because some unwell patients cannot tolerate MRI. However,

Table 3.35 Causes of intracranial haemorrhage

	Cause	Description
Intracerebral haemorrhage	Small-vessel disease	Common Fibrinoid necrosis leads to multiple 'Charcot–Bouchard microaneurysms' which bleed (leukoaraiosis and lacunes in imaging are clues) Tend to be deep, in basal ganglia and thalamus
	Cerebral amyloid angiopathy	Common in elderly Linked with dementia, but often no history of dementia Affects cortical rather than deep vessels Tends to result in recurrent lobar bleeds or microbleeds Outcome good but recurrence is common
	Arteriovenous malformation	Conglomerate of abnormal arteries and veins, often without normal capillaries between Bleeding usually lobar, from a single arteriovenous malformation Often younger people Strong association with subarachnoid haemorrhage and bleeds into Sylvian or inter-hemispheric fissues Occasionally part of hereditary haemorrhagic telangiectasia A large arteriovenous malformation can also cause stroke by 'stealing blood' from another territory
	Cavernous malformation	Personal or family history of intracerebral haemorrhage or seizures Usually small lobar haemorrhages that do not extend into other compartments
	Intracranial venous thrombosis	Associated with pregnancy, thrombophilia or inflammatory disease Intracerebral haemorrhage close to venous sinuses and cortical veins
	Dural arteriovenous fistula	Associated with pulsatile tinnitus Intracerebral haemorrhage close to venous sinuses and cortical veins
	Haemorrhagic transformation of infarct	Deterioration following recent infarct
	Coagulopathy	Often bleeding at other sites
	Neoplasm (primary or metastatic)	Sometimes the first presentation
	Vaculitis	Systemic vasculitis Lymphocytes in cerebrospinal fluid
	Infective endocarditis	Septic embolisation leading to 'mycotic' aneurysm formation
	Hypertensive encephalopathy	Evidence of accelerated hypertension
	Undisclosed trauma	Alcohol may have been involved
	Drugs	Amphetamines, cocaine, sympathomimetic drugs
Subarachnoid haemorrhage		Unlike subdural or extradural haematoma, blood not confined to discrete area and often tracks through subarachnoid space to outer areas of brain, welling up within gyri
Subdural haematoma		Acute or chronic, the latter often a cause of reversible 'dementia' History of trauma may be minimal or unclear
Extradural haematoma		Usually soon after obvious trauma Sometimes lucid period before rapid decline

improvements in MRI are leading to it superseding CT as the most favourable test because it can now give rapid positive diagnoses rather than simply excluding haemorrhage. Three areas of information may be useful in stroke imaging.

Imaging vascular occlusion

This is still not crucial until or unless direct angiographic intervention is possible. Traditional angiography is seldom performed. CT angiography shows occluded vessels as hyperdense or white; mimics include a raised haematocrit, microcalcification or hypodense parenchyma giving the appearance of hyperdense vessels, or indeed appearances may be normal, all vessels appearing whiter than usual. Magnetic resonance (MR) angiography is an alternative.

Imaging acute parenchymal infarction

CT shows loss of grey/white matter distinction before 3 hours in 50–70% of infarcts, together with obscuration of deep nuclei and loss of the insular 'ribbon'. The parenchyma is hypodense or dark. Very dark areas with encephalomalacia reflect old strokes. Gyral swelling occurs at 12–24 hours. Haemorrhagic transformation shows a variety of changes.

MRI is by a number of methods:

- T1 imaging shows loss of grey/white differentiation and early swelling.
- T2 imaging shows early swelling, hyperdense (reflecting water) change and 'fogging' at 2–3 weeks; T1 and T2 techniques differ in many subtle ways, and essentially cerebrospinal fluid is black in T1 and white in T2; infarcts are white in both, as are small vessel disease and lacunar infarcts.
- Fluid-attenuated inversion–recovery (FLAIR) images may be positive as early as 6 hours.
- Gadolinium contrast-enhanced MR images show intravascular slowing or stasis immediately, pial collaterals at 24–48 hours resolving by 3–4 days and parenchymal changes at 24–48 hours, which may persist for a few weeks.

Thus, in terms of speed of detection, CT shows blood immediately but may miss smaller infarcts and may be difficult to interpret in the first few hours; T1, T2 and FLAIR imaging show infarcts at 6–12 hours. But modern treatment of stroke requires earlier detection and MR diffusion-weighted imaging (DWI) has improved the detection of infarcts to within 1 hour and perfusion imaging by CT or MRI can detect infarcts immediately. Diffusion imaging is based on water molecule movement; as cerebral blood flow slows, there is failure of sodium membrane pumps, leading to oedema. DWI is abnormal within 30–60 minutes of an infarct, abnormalities peaking at 2–3 days and normalising at around 1 month. The size of the infarct on DWI is proportional to outcome. Furthermore, DWI also detects many small infarcts previously attributable to TIAs.

Imaging reversible ischaemia

Cerebral blood flow is the gold standard method of detecting this. This may be by CT or MRI, either requiring rapid repeat slices for 40 seconds to detect perfusion defects or perfusion/diffusion mismatch. Thus, DWI detects infarction and perfusion-weighted imaging (PWI) identifies what is potentially salvageable.

What pitfalls might there be when imaging in acute stroke?

Apart from the difficulties in early diagnosis, vascular territories are very variable, and odd variants include, for example, a dominant posterior cerebral artery arising from an internal carotid artery, leading to apparent middle cerebral artery occlusion. Watershed infarcts occur between rather than within territories. Less common causes of infarct outlined in Table 3.34 should also be considered.

List some causes of multiple small bleeds noted on MRI

These may be detected on MRI when not apparent on CT, and include diffuse small-vessel disease, cerebral amyloid angiopathy (can produce larger bleeds), haemorrhagic metastases, septic emboli and multiple arteriovenous malformations.

Are infarcts easy to distinguish from tumours or inflammation with imaging?

Cytotoxic oedema of infarcts affects white and grey matter whereas vasogenic oedema of tumours and inflammation affects only white matter. Sometimes follow-up scanning is required to be certain.

When should brain imaging be performed in acute stroke?

Brain imaging should be performed immediately (ideally the next slot and definitely within 1 hour, whichever is sooner) for people with acute stroke if any of the features in Box 3.38 apply.

Brain imaging should otherwise be performed as soon as possible (within a maximum of 12 hours after onset of symptoms).

What are the benefits of thrombolysis in stroke?

The key is to identify the infarct early and institute treatment to limit its size by reperfusion of the ischaemic, threatened penumbra. 'Time is brain'. Penumbra gives way to cell death as oedema, lactate and perturbed neuroelectrical activity occur. There have been numerous trials of thrombolysis, e.g. NINDs, ECASS I, ECASS II, and a meta-analysis with 'intention to treat analysis' of 2775 patients (a high number for stroke evidence-based medicine). Median age was 68 years and mean National Institutes of Health Stroke Scale (NIH-SS) score was 11; one-third of

Box 3.38 **Indications for immediate brain imaging in stroke**

- Indications for thrombolysis or early anticoagulation treatment
- On anticoagulant treatment
- Known bleeding tendency
- Depressed level of consciousness (Glasgow Coma Score < 13)
- Unexplained progressive or fluctuating symptoms
- Papilloedema, neck stiffness or fever
- Severe headache at onset of stroke symptoms

patients were treated within 180 minutes and two-thirds beyond 180 minutes. The tendency was for earlier treatment in the US NINDS study (before 3 hours) and later treatment in the European ECASS studies (up to 6 hours), explaining the overall benefit seen in the former and its lack in the latter. The risk of bleeding is increased with longer time frames, with significant overall benefit within 3 hours, uncertain benefit between 3 and 4 hours and beyond 4 hours benefit crossing confidence intervals. Thrombolysis can achieve a 45% overall decrease in death or dependence, the NNT 8, comparing well with many cardiac trials. The NNT approximately doubles with each hour, 2–3 in the first hour, 6 in the second and 25 in the third. Overall bleeding rates were 5.9% but there are so many exclusion criteria in considering thrombolysis and inadvertent protocol violations were probably not uncommon. In-hospital mortality was not prevented by thrombolysis but long-term disability was. Trials to determine whether thrombolysis may be considered with longer time intervals are ongoing, and the ECASS III data suggested thrombolysis might be beneficial at 3–4.5 hours; this is now recommended for suitable patients, and indeed up to 6 hours on an individual basis.

List some important inclusion and exclusion criteria to thrombolysis in stroke

The NIH-SS is a means of scoring functional deficit, and should be incorporated into the weighing up of potential candidacy for thrombolysis; a very low score with minimal deficit is likely to improve without exposure to the bleeding risks of thrombolysis and a high score carries a high risk of bleeding because brain is 'mushier'; stroke suitable for thrombolysis is hence neither too mild nor too severe.

Scoring is from 0 to 42, < 10 being mild, 10–20 moderate and > 20 severe with thrombolysis advocated with extreme caution over 22. However, a score of 22 because of drowsiness might be considered more risky than a score of 22 with severe focal signs in an alert patient. Furthermore, a low score such as 6 or 7 might be considered worthy of thrombolysis in a PACS where extending damage might otherwise occur, but not in a LACS.

The SITS-MOST study compared the results of symptomatic ICH and death (primary endpoints) and independence (secondary endpoint) for stroke patients treated with recombinant tissue plasminogen activator (rt-PA) in routine clinical settings with those from corresponding rt-PA treated patients in randomised controlled trials (RCTs). This observational study confirmed that intravenous alteplase is safe and effective in routine clinical use when given within 3 hours of stroke onset. The inclusion and exclusion criteria used in the SITS-MOST study protocol serve as a guide for suitability of patients for referral to a thrombolysis service (Table 3.36).

Where thrombolysis is given, the NIH-SS score is repeated at 2 hours, 24 hours and 7 days, and antiplatelet therapy is withheld for the first 24 hours. Serum S100B is an astroglial protein that indicates blood–brain barrier dysfunction and is associated with increased risk of haemorrhagic transformation following thrombolysis; as yet, biomarkers are unreliable for use in practice.

Vascular causes of ischaemia not attributable to *in situ* arterial thrombosis or arterial emboli will also produce the clinical picture of ischaemic stroke and, if diagnosed, raise questions about the appropriateness of thrombolysis; conditions include venous infarction related to venous sinus thrombosis, low-flow states with associated infarction due to bilateral critical carotid stenosis, large-artery dissection causing hypoperfusion rather than embolic complications, cerebral vasculitis, and profound hypotension or hypoxia. Thrombolysis is also contraindicated in rare cases where cardiogenic thrombus has propagated to lodge itself in, for example, the brachiocephalic or subclavian artery; here, dismantling clot may produce emboli that have nowhere to go but the brain.

What are the major barriers to thrombolysis in stroke?

These include recognition of stroke, time and appropriate services being in place:

- In people with sudden onset of neurological symptoms a validated tool, such as FAST (Face Arm Speech Test), with an 85% specificity and similar sensitivity for hemispheric stroke, should be used outside hospital to screen for a diagnosis of stroke or TIA. People admitted to emergency departments with a suspected stroke or TIA should have the diagnosis established rapidly using a validated tool, such as ROSIER (Recognition of Stroke in the Emergency Room); this is particularly important in a busy and noisy department for a condition in which symptoms tend to be negative rather than positive.
- A major barrier to thrombolysis is time, which requires coordination across the NHS, e.g. public and primary care provider awareness, ambulance response times, prioritisation on arrival to hospital, immediate imaging, immediate access to a physician trained in assessing the patient and obtaining consent.
- Alteplase is recommended for the treatment of acute ischaemic stroke but should only be administered within a well-organised stroke service with staff trained in delivering thrombolysis and in monitoring for complications, and where there is immediate access to imaging and re-imaging. Staff in emergency departments, if appropriately trained and supported, can administer alteplase provided patients can be managed within an acute stroke service.

What other pharmacological treatments are important in acute stroke?

Urgent treatment has been shown to improve outcome in stroke.

Antiplatelet therapy

All people with acute stroke who have had a diagnosis of primary ICH excluded by brain imaging should, as soon

Table 3.36 Some important inclusion and exclusion criteria for thrombolysis in stroke

Inclusion	Male or female aged 18–80 years Clinical diagnosis of ischaemic stroke Onset of symptoms within 3 hours of predicted initiation of thrombolysis Stroke symptoms present for at least 30 minutes without significant improvement before commencement of therapy
Exclusion	Evidence of ICH on the CT scan Duration of symptoms > 3 hours from likely time of initiation of tPA infusion or unknown time of symptom onset Minor neurological symptoms (e.g. sensory loss only, dysarthria only, ataxia only, minimal weakness, partial visual field defect) or symptoms rapidly improving Severe stroke, as assessed clinically (e.g. coma, hemiplegia plus fixed head/eye deviation) or by appropriate imaging techniques (e.g. diffuse swelling of a cerebral hemisphere, brain swelling, sulcal effacement or parenchymal hypodensity involving > one-third of MCA territory or entire ACA or PCA territory) Seizure at stroke onset Symptoms suggestive of SAH even if the CT scan is normal Administration of heparin within the previous 48 hours and thromboplastin time above the upper limit of normal Past history of stroke *and* concomitant diabetes Previous stroke within last 3 months Known platelet count < 100 000/mm^3 Systolic BP > 185 mmHg or diastolic > 110 mmHg or the need to treat aggressively with i.v. medication to achieve these levels Blood glucose < 50 or > 400 mg/l (< 2.8 or > 22.0 mmol/l) Known haemorrhagic diathesis Warfarin therapy (although considered appropriate if INR < 1.4) Recent or current bleeding Known history of or suspected ICH Presenting symptoms and signs or disability, likely to be due to recent or past SAH Known CNS disease (e.g. neoplasm, aneurysm, past intracranial or spinal surgery) Haemorrhagic retinopathy Recent (< 10 days) traumatic external heart massage, childbirth, puncture of a non-compressible blood vessel (e.g. subclavian vein) Known bacterial endocarditis, pericarditis Acute pancreatitis Documented ulcerative GI disease during the last 3 months or oesophageal varices Neoplasm with increased bleeding risk Severe liver disease Major surgery or significant trauma in last 3 months

ACA, anterior cerebral artery; BP, blood pressure; CNS, central nervous system; CT, computed tomography; GI, gastrointestinal; ICH, intracerebral haemorrhage; INR, international normalised ratio; i.v., intravenous; MCA, middle cerebral artery; PCA, posterior cerebral artery; SAH, subarachnoid haemorrhage; tPA, tissue plasminogen activator.

as possible but certainly within 24 hours, be given aspirin 300 mg orally if not dysphagic or rectally or by enteral tube if dysphagic. Thereafter, aspirin 300 mg should be continued until 2 weeks after the onset of stroke symptoms, at which time definitive long-term antithrombotic treatment should be initiated; this usually includes lower dose aspirin, the high dose of 300 mg for the first 2 weeks compensating for early prostaglandin handling. People discharged before 2 weeks can be started on long-term treatment earlier. For previous dyspepsia with aspirin, a proton pump inhibitor is also given. For allergy or intolerance to aspirin, an alternative antiplatelet agent is given. Dipyridamole extended release (ER) 200 mg twice daily is also given to patients able to swallow, but blocks nasogastric tubes. Other antiplatelet agents are emerging as alternatives, and understanding an individual's genetic resistance to various agents may also allow more targeted treatment. Aspirin should be withheld for 24 hours after thrombolysis.

Anticoagulation

Prophylactic

Anticoagulation should not be used routinely for the treatment of acute stroke. However, there may be a subgroup of people for whom the risk of venous thromboembolism (VTE) outweighs the risk of stroke haemorrhagic transformation. People considered to be at particularly high risk of VTE include anyone with complete leg paralysis, a previous history of VTE, dehydration, or comorbidities such as malignant disease, or current or recent smokers. Such people should be kept under regular review if given prophylactic anticoagulation.

Therapeutic

Routine therapeutic anticoagulation is of no benefit and increases the risk of bleeding (International Stroke Trial).

People with disabling ischaemic stroke in atrial fibrillation should be treated with aspirin 300 mg for the first 2 weeks before anticoagulation is considered.

In people with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation, anticoagulation should be stopped for 1 week and aspirin 300 mg substituted.

People with ischaemic stroke and symptomatic proximal deep vein thrombosis or pulmonary embolism should receive anticoagulation in preference to aspirin unless there are other contraindications to anticoagulation. People with haemorrhagic stroke and symptomatic deep vein thrombosis or pulmonary embolism should have treatment to prevent the development of further pulmonary emboli using either anticoagulation or a caval filter.

People with primary ICH receiving anticoagulation before their stroke should have their international normalised ratio (INR) normalised as soon as possible by reversing the effects of the anticoagulation using a combination of prothrombin complex concentrate and intravenous vitamin K.

Antithrombotic therapy in acute venous stroke, arterial dissection and antiphospholipid syndrome

People with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) should be given full-dose anticoagulation treatment (initially full-dose heparin and then warfarin (INR 2–3)) unless there are comorbidities that preclude its use.

People with stroke secondary to acute arterial dissection should be treated with either anticoagulants or antiplatelet agents, preferably as part of an RCT.

There is insufficient evidence to support any recommendation on the safety and efficacy of anticoagulants versus antiplatelets for acute ischaemic stroke in the setting of antiphospholipid syndrome and management should be as for acute ischaemic stroke without antiphospholipid syndrome.

Blood pressure control

Trials continue to determine if and how blood pressure should be manipulated in acute stroke. Physiological arguments for treatment are that it may reduce oedema and the risk of haemorrhagic transformation and against that it may jeopardise cerebral perfusion. Traditional practice is to continue antihypertensives patients are already taking but not to escalate treatment for 2 weeks as blood pressure rises in the first few days post-stroke reflect increased perfusion pressure needs. Anti-hypertensive treatment in people with acute stroke is currently recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:

- Hypertensive encephalopathy
- Hypertensive nephropathy
- Hypertensive heart failure / myocardial infarction
- Aortic dissection
- Pre-eclampsia / eclampsia
- ICH with systolic blood pressure over 200 mmHg
- Blood pressure reduction to 185 / 110 mmHg or lower should be considered in people who are candidates for thrombolysis

Possible treatments include an intravenous nitrate infusion or intravenous boluses of labetalol followed by a labetalol infusion.

Lipid-lowering treatment

Immediate initiation of statin treatment is not recommended in people with acute stroke. The consensus is that it is safe to start statins after 48 hours (there is some evidence that early statin use, especially in high dose, increases the risk of haemorrhagic transformation). People with acute stroke who are already receiving statins should continue their statin treatment.

Blood sugar control

Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose to maintain a blood glucose concentration between 4 and 11 mmol / l, should be provided to all adults with diabetes who have threatened or actual myocardial infarction or stroke.

Maintenance or restoration of homeostasis and supplemental oxygen therapy

A key element of care for people with acute stroke is the maintenance of cerebral blood flow and oxygenation to prevent further brain damage after stroke, using the above pharmacological measures. People who have had a stroke should receive supplemental oxygen only if their oxygen saturation drops below 95% but the routine use of supplemental oxygen is not recommended in people with acute stroke who are not hypoxic.

What non-pharmacological measures are important in acute stroke?

The following are integral parts of stroke care.

Assessment of swallowing function

On admission, people with acute stroke should have their swallowing screened by an appropriately trained healthcare professional before being given any oral food, fluid or medication. If the screen indicates problems with swallowing, a specialist assessment of swallowing, preferably within 24 hours of admission and not more than 72 hours afterwards, should follow.

Nutrition and hydration

Many people with acute stroke are unable to swallow safely, and may require supplemental hydration and nutrition. People with acute stroke unable to take adequate nutrition and fluids orally should receive nasogastric tube feeding within 24 hours of admission and be considered for a gastrostomy if they are unable to tolerate a nasogastric tube. A dietitian should provide a detailed nutritional assessment, individualised advice and monitoring. The FOOD trials did not show overt evidence in favour of nutritional supplements in patients able to swallow, advocated early feeding where possible by nasogastric tube if swallowing impaired (although evidence not strong as to provoke alarm if proving an initial challenge), and showed that gastrostomy feeding was more risky than beneficial early, within the first 3 weeks.

Oral nutritional supplementation

All patients should be screened for malnutrition and the risk of malnutrition. The Malnutrition Universal Screening Tool (MUST) may be used to do this. Dysphagia, poor oral health and reduced ability to self-feed will affect nutrition in people with stroke. Routine nutritional supplementation is not recommended for people with acute stroke who are adequately nourished but should be initiated for people at risk of malnutrition. This may include oral nutritional supplements, specialist dietary advice and/or nasogastric tube feeding. All patients should have their hydration assessed on admission, reviewed regularly and managed so that normal hydration is maintained.

Early mobilisation and optimum positioning of people with acute stroke

Early mobilisation is a key element of acute stroke care. People with acute stroke should be helped to sit up as soon as possible when their clinical condition permits. Sitting up helps maintain oxygen saturations and reduces the likelihood of hypostatic pneumonia. Mobilisation should occur as soon as possible as part of an active goal-setting management programme.

Avoidance of aspiration pneumonia

Aspiration pneumonia is a complication of stroke associated with increased mortality and poor outcomes. In people with dysphagia, food and fluids should be given in a form that can be swallowed without aspiration, following specialist assessment of swallowing.

Is there a role for decompressive hemicraniectomy in acute ischaemic stroke?

People with middle cerebral artery infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy. They should be referred within 24 hours of onset of symptoms and treated within a maximum of 48 hours.

- Age ≤ 60 years
- Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the NIH-SS of above 15
- Decrease in the level of consciousness to give a score of 1 or more on item 1a of the NIH-SS
- Signs on CT of an infarct of at least 50% of the middle cerebral artery territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cm^3 as shown on diffusion-weighted MRI.

People who are referred for decompressive hemicraniectomy should be monitored by appropriately trained professionals skilled in neurological assessment.

Do you know of any potential novel treatments in ischaemic stroke?

Endovascular techniques to 'fish' or 'suck' out the clot do not yet have a sturdy evidence base. Localised intra-arterial thrombolysis may develop further. Treatments that may limit ischaemic penumbra and novel antiplatelet therapies remain under research.

What other secondary prevention measures are there after a stroke?

The risk of further stroke is highest early after stroke or TIA and may be as high as 20% within the first month and 10% within the first week. Appropriate secondary prevention should therefore be commenced as soon as possible, usually in the acute phase if safe to do so.

Lifestyle measures

This requires changes in behaviour by the patient in areas such as smoking, exercise, eating and alcohol intake. The aim should be to achieve moderate physical activity (sufficient to become slightly breathless) for 20–30 minutes each day. The optimum diet includes five or more portions of fruit and vegetables per day, two portions of fish per week, one of which should be oily (salmon, trout, herring, pilchards, sardines, fresh tuna), and replacing saturated fats with polyunsaturated or monounsaturated fats by using low-fat dairy products, replacing butter and lard with products based on vegetable and plant oils and reducing meat intake. All patients, but especially those with hypertension, should be advised to reduce salt intake.

Antiplatelet therapy

All patients with ischaemic stroke in sinus rhythm should receive antiplatelet therapy – aspirin 75–300 mg daily, clopidogrel, or a combination of low-dose aspirin and dipyridamole ER, as evidenced by the CAPRIE, ESPS-2 and ESPRIT trials and endorsed in National Institute for Health and Clinical Excellence guidelines following a first episode of stroke or TIA. Aspirin alone gives incomplete protection. Aspirin and clopidogrel in combination appears to be less beneficial in ischaemic stroke than in coronary disease and the MATCH trial showed that benefits did not outweigh risks. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study is the largest study of antiplatelet therapy after stroke or TIA, involving over 20 000 patients; it compared the combination of low-dose aspirin 25 mg plus dipyridamole ER 200 mg twice daily with clopidogrel 75 mg once daily, the former failing to show non-inferiority over the latter. ESPRIT essentially endorsed ESPS-2, which showed that aspirin and dipyridamole ER are effective in preventing recurrent vascular events, and provided a starting point of using aspirin and dipyridamole ER for most patients following stroke or TIA. However, a third of patients will not tolerate this combination, especially dipyridamole, which induces headache. Where aspirin is not tolerated, clopidogrel monotherapy in light of ProFESS is a clear alternative. The decision as to whether to continue aspirin alone in dipyridamole intolerance, which costs little and has a mass of evidence, or to use clopidogrel, which is more costly, is open to interpretation, though many would now choose clopidogrel. Treatment in those with cerebral venous sinus thrombosis, stroke secondary to acute arterial dissection and with antiphospholipid syndrome is described above. Those with recurrent TIA or stroke should probably be managed in the same way as those who have had a single event.

Anticoagulation

Anticoagulation is indicated for all patients with persistent or paroxysmal atrial fibrillation. It should not be started until brain imaging has excluded haemorrhage and usually until 14 days have elapsed from the ischaemic event; it is used instead of antiplatelet therapy.

Carotid endarterectomy

Carotid endarterectomy is the most effective intervention to prevent stroke in patients with recent symptoms of carotid stenosis. It also prevents future stroke in younger patients (under 75 years) who have not yet had symptoms, as long as the risk of stroke and death from surgery is not more than 3%. Early carotid endarterectomy should be considered as soon as possible if there is symptomatic carotid stenosis, the risk of major stroke up to 30% in the first month, falling rapidly with time, as does the benefit of endarterectomy – the NNT to prevent one major event is five in the first 2 weeks but 125 after 12 weeks. Any patient with a carotid artery territory TIA or stroke but without severe disability should be considered for carotid endarterectomy, and have a carotid duplex ultrasound performed urgently to estimate the degree of stenosis and a second urgent non-invasive imaging investigation (such as MR angiography) to confirm this. Carotid endarterectomy should be considered when carotid stenosis is measured at 50–99% or 70–99% stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and the European Carotid Surgery Trialists' (ECST) Collaborative Group, respectively. Surgical carotid endarterectomy should be undertaken in patients fit for surgery within 2 weeks of symptoms. Carotid angioplasty or stenting should only be carried out in specialist centres. Stenting has not yet been shown to be a safe alternative to endarterectomy. In the International Carotid Stenting Study (ICSS), surgery was significantly less likely than stenting to cause stroke, myocardial infarction, or death and in the Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST) results were more reassuring for stenting but the debate remains. Longer term follow-up (2–10 years) after successful carotid artery stenting and carotid endarterectomy indicates that the procedures are equally effective in preventing stroke. Arterial restenosis seems to be more likely after stenting, but it is rare to develop associated symptoms. A learning curve inevitably exists for stenting.

Blood pressure

The risk of first stroke is more or less directly related to the actual blood pressure, with no obvious threshold values in population studies. All patients should have their blood pressure checked, and should be treated in keeping with national guidelines, an optimal target with established cardiovascular disease being 130/80 mmHg but for patients known to have bilateral severe (> 70%) internal carotid artery stenosis a slightly higher target (e.g. systolic blood pressure of 150 mmHg) may be appropriate. Blood pressure reduction should be undertaken as per blood pressure guidelines. PROGRESS was a secondary prevention multi-centre RCT of over 6000 patients with stroke or TIA in the previous 5 years. Active treatment comprised perindopril alone or in combination with indapamide (added at the clinician's discretion). Combination therapy achieved a relative stroke risk reduction of 28% after 4 years. The risk of fatal or disabling stroke was reduced by 24%, ischaemic stroke by 24% and cerebral haemorrhage by 50%. A further study by the PROGRESS Collaborative Group found that treatment also substantially reduced adverse cardiac outcomes. PROGRESS showed a mild mean blood pressure reduction (12/5 mmHg) with combination treatment, perindopril alone 5/3 mmHg with no significant effect on stroke or other vascular events, but suggested that the lower the blood pressure in stroke secondary prophylaxis the better and that there may be a benefit in treating normotensive patients. Angiotensin-converting enzyme inhibitors probably protect by many mechanisms, including reduction of oxidative stress, regulation of pro-inflammatory cytokines, decreased progression of atherosclerotic plaques and plaque stabilisation.

Lipid-lowering therapy

All patients (especially if total cholesterol is above 3.5 mmol/l or low-density lipoprotein (LDL) cholesterol is above 2.5 mmol/l) who have had an ischaemic stroke or TIA should be treated with a statin unless contraindicated, with treatment goals a total cholesterol < 4.0 mmol/l and LDL cholesterol < 2.0 mmol/l, or a 25% reduction in total cholesterol and a 30% reduction in LDL cholesterol, whichever achieves the lowest absolute value. The SPARCL trial and the Cholesterol Treatment Trialists' Collaboration found that high doses of statins reduced vascular events including ischaemic stroke by around 30%.

Oral contraception and hormone replacement therapy

Primary prevention studies indicate that there may be an approximate doubling of the relative risk of ischaemic stroke in women using combined (low-dose) oestrogen oral contraception. The combined oral contraceptive pill should not be routinely prescribed following ischaemic stroke. Some women who have had a stroke may wish to continue with hormone replacement therapy for control of symptoms and an enhanced quality of life.

How might rehabilitation help stroke patients?

Rehabilitation should not be underestimated because the brain has much plasticity and neuronal reserve needs encouragement. It should start in the acute phase, ideally from day 1 or day 2. Goal-setting is fundamental to rehabilitation.

Physiotherapy

The roles of physiotherapy are many and include:

- Gait retraining, treadmill retraining, and walking aids
- Strength training – resisted exercise
- Balance training
- Orthoses use, positioning, splinting and stretching (to prevent and treat contractures).

Physiotherapists can also help with impaired motor control, and impaired tone. In patients with persistent troublesome focal spasticity affecting one or two joints intramuscular botulinum toxin may alleviate the problem. This should be accompanied by rehabilitation therapy. For patients experiencing troublesome general spasticity, antispastic drugs – baclofen, gabapentin or tizanidine – may help. Robotics refers to the use of automated devices controlled by microprocessors that can move a limb (or more) and are increasingly used. About 70% of patients will experience altered arm function after a stroke, and arm therapies include techniques such as constraint-induced movement therapy in selected cases. Functional electrical stimulation (FES) is based on the principle that, where the brain cannot control muscles, electrical stimulation of the relevant nerve (or, rarely, muscle) might be able to increase function; FES is not used routinely but is sometimes useful in foot-drop and painful shoulder subluxation – a common problem in stroke.

Neglect, agnosia, apraxia and executive dysfunction

Any patient with neglect or spatial awareness problems should be given cues to draw attention to the affected side, monitored to ensure that they eat enough, and given trials of visual scanning training and mental imagery training.

Some patients have perceptual problems, including a specific difficulty in recognising objects, especially visual agnosia (other agnosias are very rare); compensation strategies may be taught.

Apraxia refers to the loss or disturbance of the conceptual ability to organise actions, and is usually associated with damage to the left cerebral hemisphere; compensation strategies may be taught.

The 'dysexecutive syndrome' encompasses several impairments including difficulties with planning, organising, initiating, and monitoring behaviour; in stroke these are relatively rare, but are seen more commonly after subarachnoid haemorrhage with secondary frontal lobe infarction; compensation strategies may be taught.

Occupational therapy

This assumes greater importance as patients are rehabilitating.

Speech and language and swallow therapy

This is vital in aphasia, dysarthria and dysphagia; a few patients have apraxia of speech.

Visual impairment

Visual impairment, including the common homonymous hemianopia; compensation strategies may be taught.

Other

These include management of bowel and bladder problems, pain management (neuropathic pain or central post-stroke pain, and musculoskeletal pain), depression, anxiety and emotionalism management, and management of cognitive impairment. Driving advice should not be forgotten.

Should a patent foramen ovale (PFO) be closed in stroke?

A PFO is present in around 25% of people. It is often not an isolated phenomenon and the spectrum of abnormalities includes a simple flap, an oval fossa, a fenestrated piece of tissue and a PFO with additional abnormalities as in an aneurysmal PFO with an atrial septal defect or atrial septal abnormality (ASA). The best test to detect a PFO is echocardiography with contrast, either transthoracic or transoesophageal. PFOs are associated with numerous clinical problems, the two most notable of which are stroke and migraine.

Stroke

There is no robust evidence to inform best strategy. Epidemiological studies suggest an odds ratio of PFO as a risk factor for stroke of 1.83. In those < 55 years the odds ratio rises to 3.1. In those with PFO < 55 years and cryptogenic stroke the odds ratio rises to 6, and the role of ASA in cryptogenic stroke pushes that odds ratio up to around 23. Thus it appears that the combination of cryptogenic stroke, age < 55 years and PFO +/− ASA places people at considerable risk and that this would intuitively seem a group to target for preventive treatment, especially those with a large PFO. It also seems that transcatheter closure of a PFO is able to prevent a substantial proportion of cryptogenic strokes. The risk of recurrent stroke in people with a PFO is unclear, with conflicting data, and the influence of treatment on recurrent stroke in patients with PFO is unclear. There is no worrying evidence of harm from PFO closure but trials are fraught with recruitment difficulties. The American Heart Association/American Stroke Association Council on Stroke recommend that, following an ischaemic stroke or TIA with a PFO present, antiplatelet therapy should be standard, with anticoagulation reserved for patients at high risk such as those with evidence of venous thrombosis or those with a hypercoagulable state. There are insufficient data to recommend PFO closure in first stroke, but it may be considered for recurrent cryptogenic stroke despite optimal medical therapy. The risk–benefit ratio is not based on robust evidence but clinical factors dictating closure include preceding Valsalva manoeuvre, a prothrombotic state and multiple events and echocardiographic factors dictating closure include a large amount of shunting, shunting at rest and the presence of an ASA. An older person with a stroke and TIAs, traditional risk factors and a PFO should be offered conventional treatment and not offered PFO closure. Those with a PFO should probably wear compression stockings, ensure good hydration and regular mobilisation, and take aspirin on long-haul flights.

Migraine

There is strong circumstantial evidence of a link between migraine with visual aura and large shunts. There is also substantial evidence that PFO closure produces improvement in symptoms, although evidence to date suggests that this is not complete resolution of symptoms but a reduction in symptoms or symptom frequency, although this is not guaranteed for individual patients. A young woman with frequent migraine with aura, a large PFO and ASA might thus be offered closure on the basis that it might reduce symptoms. Closure should be safe in experienced hands but this requires someone who does hundreds of these procedures.

How should ICH be investigated?

After a radiological diagnosis of ICH, some routine investigations are essential – blood tests including coagulation screen and inflammatory markers, for example, but international guidelines lack consensus on which patients to image further, and how and when to do so. Early CT angiography is a first-line investigation for an underlying aneurysm or arteriovenous malformation or fistula when suspected, and arteriovenous malformations are likely to be underdiagnosed because catheter angiography is not widely used. MRI is useful for detecting venous thrombosis acutely and for detecting underlying tumours and cavernous malformations at least 2 months after ICH. It can also detect some foci of haemosiderin, known as microbleeds, but the diagnostic importance of their detection is unclear.

How should ICH be managed?

Patients with spontaneous ICH should be managed in a stroke unit, or in an intensive care unit if they need ventilation or intracranial pressure monitoring, with the same supportive care with respect to hydration, nutrition, hyperglycaemia, hyperthermia, prevention of complications, and early rehabilitation. They should be monitored for deterioration in function and referred immediately for repeat brain imaging when necessary. There is no evidence for prophylactic antiepileptic drugs, corticosteroids, mannitol, glycerol or other perceived neuroprotectants. Evidence on how blood pressure should be managed is sparse and treatment seems necessary if there is end-organ damage. Vasodilators seem theoretically risky agents because of cerebral oedema.

Haemostatic drugs

Because ICH volume influences outcome and about a third of acute ICHs enlarge within 24 hours of onset, early treatment with a haemostatic drug might improve outcome by limiting haematoma expansion. Trials of intravenous recombinant activated factor VII remain inconclusive.

Neurosurgical haematoma evacuation

Evacuation may show the underlying cause in the cavity or identify amyloid angiopathy if cortical biopsy is performed, but the main question is whether surgery improves outcome. Management is often supportive but neurosurgeons should be consulted unless the situation is hopeless or the ICH is clearly inaccessible, and a neurosurgical team may provide optimum supportive care even where surgery is inappropriate. Outcomes are best in patients who are awake before the intervention (Glasgow Coma Score > 8), younger and where the ICH is superficial. Any anticoagulation should be reversed.

■ **Infratentorial ICH.** Neurosurgical intervention should be considered immediately for people with a cerebellar haemorrhage causing deterioration in consciousness, brainstem compression, or hydrocephalus as a result of obstruction of the drainage pathways for cerebrospinal fluid. Ventricular drainage may be sufficient to alleviate hydrocephalus, but further neurological deterioration requires haematoma evacuation. Pontine haemorrhages are not an indication for surgery.

■ **Supratentorial ICH.** Systematic reviews have shown conflicting results. About 14 patients with supratentorial ICH might need neurosurgical evacuation for one to avoid death or dependence, but estimates are not robust. A subgroup of patients with superficial lobar ICH within 1 cm of the cortical surface seemed to benefit in the STICH trial, studied further in STICH II.

People with any of the following rarely require surgical intervention and should receive initial medical treatment:

- Small deep haemorrhages
- Lobar haemorrhage without either hydrocephalus or rapid neurological deterioration
- A large haemorrhage and significant comorbidities before the stroke
- A Glasgow Coma Scale score < 8 unless this is because of hydrocephalus
- Brainstem haemorrhage.

Previously fit people should be considered for surgical intervention following primary ICH if they have hydrocephalus.

Treatments of causes

Some causes of ICH should not be missed because treatment may improve outcome:

- Aneurysms and arteriovenous malformations that have bled may benefit from immediate evacuation of the haematoma with concomitant aneurysm clipping. A large trial of coiling versus clipping showed that coiling is less likely to result in death at 5 years despite a higher risk of re-bleeding. Trials for ruptured arteriovenous malformations or cavernous malformations are lacking, and primary prevention evidence is awaited.
- Intracranial venous thrombosis may benefit from anticoagulation (for cortical vein or venous sinus thrombosis). Expert opinion favours it, as it does not seem to precipitate or worsen clinically important ICH.
- ICH associated with antithrombotic drugs should generally be managed by stopping anticoagulants and urgently reversing their effects (the correct drug is not clear – intravenous vitamin K is slow to act, so prothrombin complex concentrate or fresh frozen plasma are given to immediately replenish vitamin K-dependent coagulation factors). But the benefits of antiplatelet or even anticoagulant drugs may outweigh their risks.
- Infective endocarditis must be treated to prevent recurrent septic emboli causing cerebral mycotic aneurysms and ICH.

Secondary prevention

Stopping smoking and limiting alcohol are important. Evidence supports a 76% reduction in secondary ICH with 12 mmHg drop in blood pressure.

What is the outcome after ICH?

Mortality is around 50% in the first month, with most survivors disabled. The main predictors of death within 1 month are older age, low score on the Glasgow Coma Scale on admission, increasing volume of ICH, infratentorial ICH, and intraventricular extension. These five prognostic factors may help to assess the risk of death within 1 month using a score called the total ICH score. Early neurological deterioration may be due to perihaematomal oedema or haematoma expansion, which affects about a third of patients within the first 24 hours. The location and cause of an ICH partly determine the long-term risk of recurrent ICH, dependence and death. Annual risk of recurrence is about 2% for deep ICH without an identified cause and 10% for lobar ICH whilst from a ruptured arteriovenous malformation it varies from about 4% to about 34% according to its vascular anatomy. People with ICH are also at increased risk of ischaemic stroke.

What is ‘phantom limb syndrome’ and what insights does it give us into brain plasticity?

This refers to the sensory appreciation of a limb that has been amputated. At first sight this seems illogical, and phantom limb ‘pain’ was once considered to be a psychological grief reaction. But take a closer look at Penfield’s homunculus (see Fig. 3.68). The entire surface of the body is repeatedly mapped on the opposite hemisphere, one such map is the post-central gyrus, like a little person draped on the surface of the brain. For the most part, it is continuous, but a discrepancy is that the face is next to the hand, rather than next to the neck. Nobody knows why, although it may relate to feeding. If a hand or arm is amputated, its cortical representation is not receiving signals, and is open to alternative sensory input, and it seems that in phantom limb syndrome sensory input from adjacent cortical areas, in this case the face, invades the vacant territory corresponding to the missing hand or arm, and is then misinterpreted in higher centres – touching the cheek, for example, may feel like touch to the thumb. The broader implications of this phenomenon relate to rehabilitation, the brain’s plasticity being increasingly understood.

Do you know of any predictors of poor outcome after stroke?

In the early phases of stroke, high temperature, low oxygen saturation and hyperglycaemia are all associated with worsening outcomes. These may, however, reflect stroke severity although it makes sense to correct these. Despite advances in acute care and rehabilitation, overall prognosis in stroke remains unsettlingly poor; 20–30% of patients die within a month and 13% of survivors are placed in care at discharge. Indeed this may rise as the older population gets older, and more strokes occur in more vulnerable brains of more fragile people. Functional status at 6 months, independent of age or type of stroke, influences prognosis – median survival is 9.7 years if independent, 6 years if dependent. The key is early treatment to reduce dependency in the early days, weeks and months, a major contributor to which is stroke unit care.

CASE 3.28 DYSPHASIA AND DYSARTHRIA

Instruction

Please examine this patient’s speech.

Recognition

There is *word-finding difficulty* and there appears to be an element of *receptive dysphasia*. Articulation appears to be mostly intact although speech is a little slurred at times.

Interpretation

Confirm the diagnosis

The findings suggest dysphasia, a cortical lesion, of language. An element of dysarthria is sometimes present owing to facial weakness after a stroke.

What to do next – consider causes / assess other systems

Tell the examiners that the most common cause is a left cortical stroke and that you would like to assess visual fields and limb function.

Consider severity / decompensation / complications

Tell the examiners that you would wish to arrange a swallow assessment and be concerned about the risk of aspiration.

Consider function

Tell the examiners that you would ensure assessment by a speech and language therapist. Mention if there is a nasogastric tube or percutaneous gastrostomy tube *in situ*. Tell the examiners that you would assess reading and writing if there were word-finding difficulty as problems with other aspects of language such as reading and writing (dyslexia and dysgraphia) are common.

Discussion

What is dysphasia?

Dysphasia (see also Examination section on speech and language) refers to the inability to understand or find words due to a lesion in the dominant (usually left) hemisphere. It is unusual for pure word-finding difficulty to exist without an element of receptive dysphasia, often unmasked by more complicated sequences of commands.

What is dysarthria?

Dysarthria (see also Examination section on speech and language) refers to impaired articulation and is the result of a lesion in any of the structures coordinating voice production – upper motor neuron lesion (pseudobulbar palsy), extrapyramidal lesion, cerebellar lesion, lower motor neuron / cranial nerve lesion (bulbar palsy), neuromuscular junction lesion (myasthenia), myopathy or local lesion of the palate, tongue or lips.

CASE 3.29 PSEUDOBULBAR PALSY

Instruction

This 65-year-old man has some speech difficulties. Please examine his speech.

Recognition

There is *dysarthria*. The *tongue appears small and 'tight'*, and cannot be protruded, lying immobile on the floor of the mouth. There is *no word-finding difficulty* and comprehension appears to be fully intact with *no evidence of receptive dysphasia*. There might be a positive jaw jerk, but this is an unreliable sign (Fig. 3.71).

In some patients there may be more complete dysarthria or anarthria with difficulty even opening the mouth and drooling, and this can very much resemble a bulbar palsy.

Interpretation

Confirm the diagnosis

Try to distinguish a bulbar from a pseudobulbar palsy although this is not always so easy in practice.

What to do next – consider causes / assess other symptoms

Common causes of a pseudobulbar palsy are listed in Box 3.39.

Box 3.39 **Common causes of a pseudobulbar palsy**

- Bilateral (usually disseminated in time) strokes – cortical or brainstem
- Demyelination

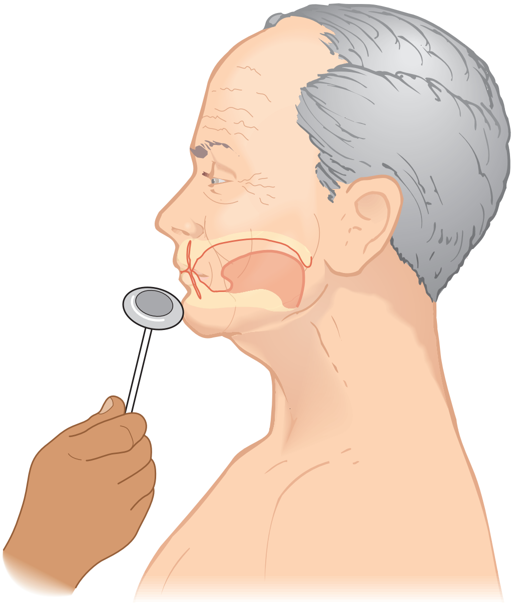


Figure 3.71 Pseudobulbar palsy.

Consider severity / decompensation / complications

Tell the examiners that you would wish to arrange a swallow assessment and be concerned about the risk of aspiration.

Consider function

Tell the examiners that you would ensure assessment by a speech and language therapist. Mention if there is a nasogastric tube or percutaneous gastrostomy tube *in situ*.

Discussion

Explain the difference between a bulbar palsy and a pseudobulbar palsy

This is explained in Box 3.25.

CASE 3.30 AGNOSIAS AND APRAXIAS

Instruction

Please examine this woman's arms and visual fields and comment on any higher cortical disturbance.

Recognition

There is *left-sided upper motor neuron weakness*. There is a *left homonymous hemianopia*. There appears to be some *sensory inattention or neglect of the left side* (Fig. 3.72). (This can make visual field testing difficult.)

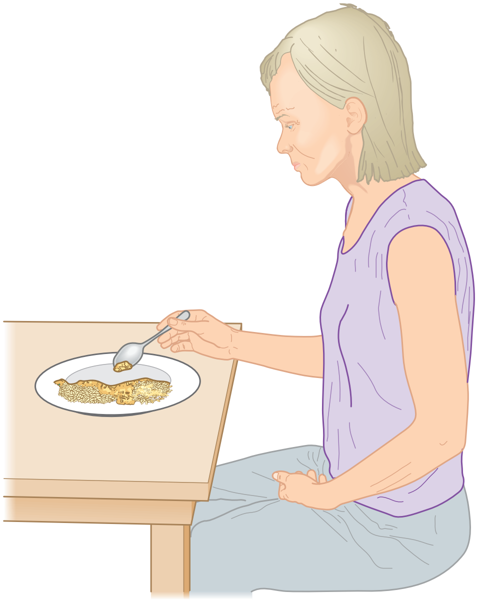


Figure 3.72 Parietal neglect or inattention.

Interpretation

Confirm the diagnosis

Ask the patient to touch their left ear with their right hand (the tendency is to touch the right ear). Ask the patient to close their eyes and tell you which hand you are touching; stroking both hands, the patient is likely to report touch only to the right hand.

What to do next – consider causes

Parietal lobe signs are common after stroke but can also be due to space-occupying lesions.

Consider severity / decompensation / complications

Tell the examiners that the combination of weakness, homonymous hemianopia and sensory inattention suggests a right total anterior circulation syndrome.

Consider function

Sensory inattention is a considerable challenge to rehabilitation.

Discussion

What is meant by the term agnosia?

This refers to difficulty recognising things, despite intact sensory pathways from periphery to parietal lobe, and results from parietal lobe damage, most commonly the non-dominant lobe. Some important agnosias are described in Table 3.37.

What is prosopagnosia and does it give any insights into the mechanisms of visual processing?

Prosopagnosia, or 'face blindness' illustrates a not uncommon agnosia. It is caused by damage to a structure called the fusiform gyrus in the temporo-parietal area. Patients are not 'blind' (they can still read), but simply cannot recognise people's faces. Much less common, but intriguing, is Capgras' syndrome, in which a patient can recognise faces but not make the association with familiarity. A patient might recognise his wife but say 'doctor, she looks like my wife but she is not; she is an imposter'. Capgras' syndrome explains the intricate steps in visual recognition well. Images are relayed via the optic nerve, optic tracts and optic radiations to around 30 visual areas at the back of the brain for analysis. After analysing all of the individual features, such as shapes, colours and textures, identification takes place in the fusiform gyrus – 'is it my wife, or somebody else, or a tiger or a wolf?' – the structure at fault in prosopagnosia. Once the image is recognised, a message is sent to the amygdala, the gateway to the limbic system, the brain's emotional core, which judges the emotional significance of the image – 'is it family, friend or foe, predator or prey, or something insignificant like a

Table 3.37 Some important agnosias

Agnosia	Description
Sensory inattention or neglect	Neglect or unawareness of one side of body, invariably left side Lesion in dominant right parietal lobe *Autotopagnosia* refers to inability to identify parts of body *Anosagnosia* refers to unawareness of any disability
Tactile agnosia (astereognosis)	Inability to recognise an object placed in the hand with the eyes closed, e.g. a key; this despite intact sensory pathways from hand to brain and motor pathways from the brain allowing adequate manipulation of the object; opening the eyes or rattling the key may prompt recognition. Lesion in contralateral parietal lobe *Agraphaesthesia* refers to inability to interpret numbers stroked on palm of the hand
Visual agnosia	Inability to recognise familiar object by sight, despite intact visual pathways to occipital lobe; touching object may prompt recognition. Lesion in contralateral parieto-occipital area *Prosopagnosia* refers to inability to recognise a familiar face
Auditory agnosia	Inability to recognise familiar sounds, e.g. voices, music, telephone

cloud in the sky?' Capgras' syndrome implies a disconnection between vision and emotion. Lending weight to the theory is that a separate pathway connects the auditory cortex in the superior temporal gyrus to the amygdala, so that if the patient hears his wife on the telephone, the auditory–emotional recognition mechanism kicks in immediately. The emotional response to visual images is fascinating as it represents the foothills in our understanding of how we, as humans, probably unlike other species, appreciate and respond to art, aesthetics and beauty.

Where is the visual external world perceived in the brain?

It is a fallacy that there is an image inside the eyeball that excites photoreceptors on the retina and then that image is transmitted faithfully along the optic nerves, tracts and fibres and displayed on a screen that is the visual cortex in the occipital lobe. Obviously, you would need a little person inside the brain to watch the image, and another to look inside his or her brain and so ad infinitum with an endless regress of little people watching images without really solving the problem. So we must think instead of representations of the external world. There is not just one visual area, the visual cortex; there are around 30 at the back of the brain that allow us to perceive the world and make sense of a bunch of green and yellow foliage and decipher whether or not the yellow pieces are lion fragments obscured by a bush. One area called V4 is involved with colour processing and another called the middle temporal (MT) area in the parietal lobe with sensing movement. When V4 is damaged bilaterally, cortical colour blindness or achromatopsia results, in which only shades of grey are seen, but there is no difficulty in reading a book, recognising faces or sensing movement. Dogs and many animals are thought to only see shades of grey, because they lack V4, although obviously dogs cannot read books either. People with MT damage cannot sense movement and might be terrified to cross the street but can read books, recognise faces and see colour.

There are, in fact, two evolutionary visual centres. The old centre, the superior colliculus in the brainstem, is the ancient one, present when we were fish. The new one is what we understand as representing vision today, the visual cortex. The old pathway is involved in locating an object in the visual field, swivelling the eyeballs and head and directing the high-acuity central foveal region of the retina towards it. The new, visual cortex is for identifying objects and generating appropriate responses.

Blind-sight is an unusual condition in which there is damage to the visual cortex on one side leading to blindness in the contralateral visual field. Patients cannot 'see', or at least consciously see, but if asked to touch your finger in the 'bind' visual field might do so accurately. It seems that the old pathway, via links to the parietal lobe, allows identification without conscious awareness. In a sense, we all have blind-sight. We might switch off awareness when watching a lion on television but were a real lion to enter the living room, the old visual pathway would rapidly alert us!

How do these processes explain sensory inattention or neglect?

Sensory inattention or neglect, in a sense, is the opposite of blind-sight (if blind-sight implies appreciation of the world without cortical vision, then neglect implies failure to appreciate part of that world even though it may be seen), but much more common. Cortical vision is intact, but when the right parietal lobe is damaged the left side of the body, as well as often paralysed, is ignored, not recognised as existing. It is a challenge to rehabilitation, and it is vital to continually encourage the brain's plasticity and stimulate the left side; visitors, for example, should be encouraged to sit at the left. We might postulate what might happen were a mirror held up to the patient's right side, so that the patient could see the reflection of their left. We might expect one of two reactions – sudden realisation of a half a world hitherto ignored, or nonchalance that although the left is represented it does not exist in the patient's world and can be ignored. In fact, if asked to touch an object on the left with the aid of a mirror, neither happens. The patient reaches into the mirror and tries to capture it through it, something a young child or even a chimpanzee realises futile. It has been termed 'mirror agnosia' or 'looking glass syndrome', since Alice walked into her world through a mirror; patients seem aware that it is a mirror, that they are seeing a reflection, and that the object is on their left, but because left does not exist in their world, all knowledge of laws of physics are disbanded to accommodate this strange new sensory world into which they have emerged.

Why is inattention not explained by a visual field defect?

Patients with sensory inattention often have a left homonymous hemianopia (especially if they have a right total anterior circulation syndrome), compounding their difficulties. In broad terms, if there is a problem with the eyes or the visual pathways then a patient is blind, either completely or partially, as in the case of left homonymous hemianopia. If there is a problem with the visual cortex then a patient is blind because of failure of visual processing (albeit potentially with 'blind-sight' alluded to above). If there is a problem with the right parietal lobe, whilst visual pathways might be intact, these are over-ridden by the failure of awareness produced by the diseased right parietal lobe; this is illustrated by the fact that, even with a right homonymous hemianopia, patients with left parietal lobe disease (the left parietal lobe not so crucially allied with visuospatial awareness) can still turn their heads to the right and are aware of their right side whereas this is not so with patients with a diseased right parietal lobe.

What is anosagnosia?

Sometimes patients with right parietal damage do not have neglect but do deny that their left side is paralysed. This is called anosagnosia. It may be that the left hemisphere's coping style is to ignore discrepancies, pretend they do not exist and forge ahead whilst the right is highly sensitive to discrepancies. So if the right parietal lobe is damaged, the left simply gets on with things as if nothing has happened, whereas if the left is damaged the right is very aware of what has happened. Even more interesting is the concept of mirror neurons. It is sometimes the case that patients with denial will deny the paralysis of other patients on the ward! Cognitive neuroscientists are learning that, just as motor command neurons are stimulated by certain actions, they can also be stimulated in observers of those actions. This 'mirror neuron' activity probably has vital roles in learning, and in reading other people's expressions, intentions and actions.

How does the body perceive pain?

Pain sensation is a vital evolutionary mechanism for survival. That nerve fibres to the spinothalamic tracts carry pain sensation is what we all learnt at medical school. What happens beyond is interesting. Signals are first relayed, via the thalamus, to the insular cortex in the temporo-parietal area, and thence to the amygdala, and especially the part of the amygdala called the anterior cingulate, where the emotional response to pain is seated, such that pain produces an appropriate response. One part of the brain signals danger, the other formulates a response.

What is meant by the term apraxia?

Apraxia refers to the loss or disturbance of the conceptual ability to perform tasks – such as combing hair, brushing teeth or writing – usually associated with damage to the left cerebral hemisphere. There is not damage to sensory pathways, motor pathways or adjustment pathways (cerebellum and extrapyramidal system), which all work normally, but failure of the parietal lobe to process information. Some important apraxias are described in Table 3.38.

An important specific syndrome of the dominant parietal lobe is Gerstmann's syndrome.

Gerstmann's syndrome

- Agraphia (inability to write)
- Alexia (inability to read)
- Finger agnosia / acalculia (inability to name and count fingers)
- Right–left agnosia (inability to determine right from left)
- Problems with numeracy (e.g. recounting serial 7s) more commonly seen as part of global cortical decline in dementia

Table 3.38 Some important apraxias

Apraxia	Description
Dressing apraxia	e.g. inability to put on pyjama top, especially if turned inside out
Gait apraxia	Inability to put one foot in front of the other, sensation of ground, and motor mechanisms of walking and balance, normal Problem may be in parietal lobe itself or in its connections with the frontal lobe or extrapyramidal system; may be overcome if other parts of brain compensate, e.g. patient may be able to walk if looks at the ground – 'the cracks between paving slabs' provide assisted visual input
Topographic apraxia	Inability to appreciate geography, e.g. patient might not be able to find way back to bed
Constructional apraxia	Inability to construct shapes or patterns using, for example, matchsticks or wooden blocks, and inability to copy shapes such as a five-pointed star or fill in numbers on a clock face
Ideomotor apraxia	Inability to perform a task automatically but not on command
Ideational apraxia	Inability to perform a series of tasks

What is synaesthesia?

Synaesthesia literally means a mixing of senses. Colour and number mixing is not uncommon, such that numbers or sequences such as days of the week or months of the year appear to be coloured. The fusiform gyrus of the temporal lobe contains the colour area V4, which processes colour information, and it so happens that the number-processing area is right next to it. It may be that 'cross-wiring' or lack of pruning of neurons in early life associates each number with a colour, and this is highly preserved, unchanging and indelible throughout one's life. It was once thought that such people should be locked away! Happily, science advances and so does understanding. It is now appreciated that there are also 'higher' synaesthetes who probably have 'cross-wiring' higher up in the temporo-parietal–occipital junction of the brain, in the vicinity of the angular gyrus, and this is the concept area of a number or day of the week or months of the year; in such people, rather than the appearance of numbers or words, it is the abstract concept or thought that provokes the sensation. Some people even perceive multi-colour and shapes and movements. Synaesthesia can involve much more elaborate mixtures such as hearing colour. What is fascinating is that people with synaesthesia tend to be more prone to using metaphors, thinking in abstract ways and lateral thinking; it is seven times more common in novelists and artists.

CASE 3.31 POSTERIOR CIRCULATION STROKE SYNDROMES

Instruction

Please examine this woman's eye movements and limbs and report your findings.

Recognition

There is a large range of brainstem and vertebrobasilar syndromes, many comprising a pot pourri of motor or sensory long tract, cranial nerve and cerebellar signs. Common symptoms and signs of posterior circulation stroke syndromes are outlined in Box 3.40.

A key feature of brainstem pathology is a constellation of symptoms or signs. The presence of one symptom or sign alone occurs in less than 1% of brainstem strokes; vertigo, for example, with no other symptoms, is more likely to have a peripheral cause. This is because structures are clustered together in the brainstem, its long tracts and nuclei like the grid of streets of New York City or London unlike the greater plains or open landscapes of the cortex.

Broadly, syndromes may be cerebellar, midbrain, pontine or medullary, or a combination of these, but may also be posterior cerebral. Two well-described syndromes are Weber's syndrome and lateral medullary (or Wallenberg) syndrome, the latter classically the result of occlusion of the posterior inferior cerebellar artery, but it may represent a variety of occlusions, and even lateral medullary syndrome exhibits variations on a theme (Fig. 3.73). The corticospinal tracts are spared in a true lateral medullary syndrome because the lesion is isolated to the dorsolateral area of brainstem.

Box 3.40 Common symptoms and signs in posterior circulation strokes

Symptoms

- Vertigo
- Headache
- Diplopia
- Loss of vision
- Ataxia (may be bilateral)
- Numbness (may be bilateral)
- Weakness (may be bilateral)

Signs

- Limb weakness
- Ataxia of gait or limbs
- Ocular palsies
- Oropharyngeal dysfunction

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about onset. Strokes are abrupt. Tell the examiners you would arrange neuroimaging to confirm and characterise stroke and exclude stroke mimics.

What to do next – consider causes

Consider the causes and risk factors described in Case 3.27.

Consider severity / decompensation / complications

Tell the examiners you would listen for signs of aspiration pneumonia.

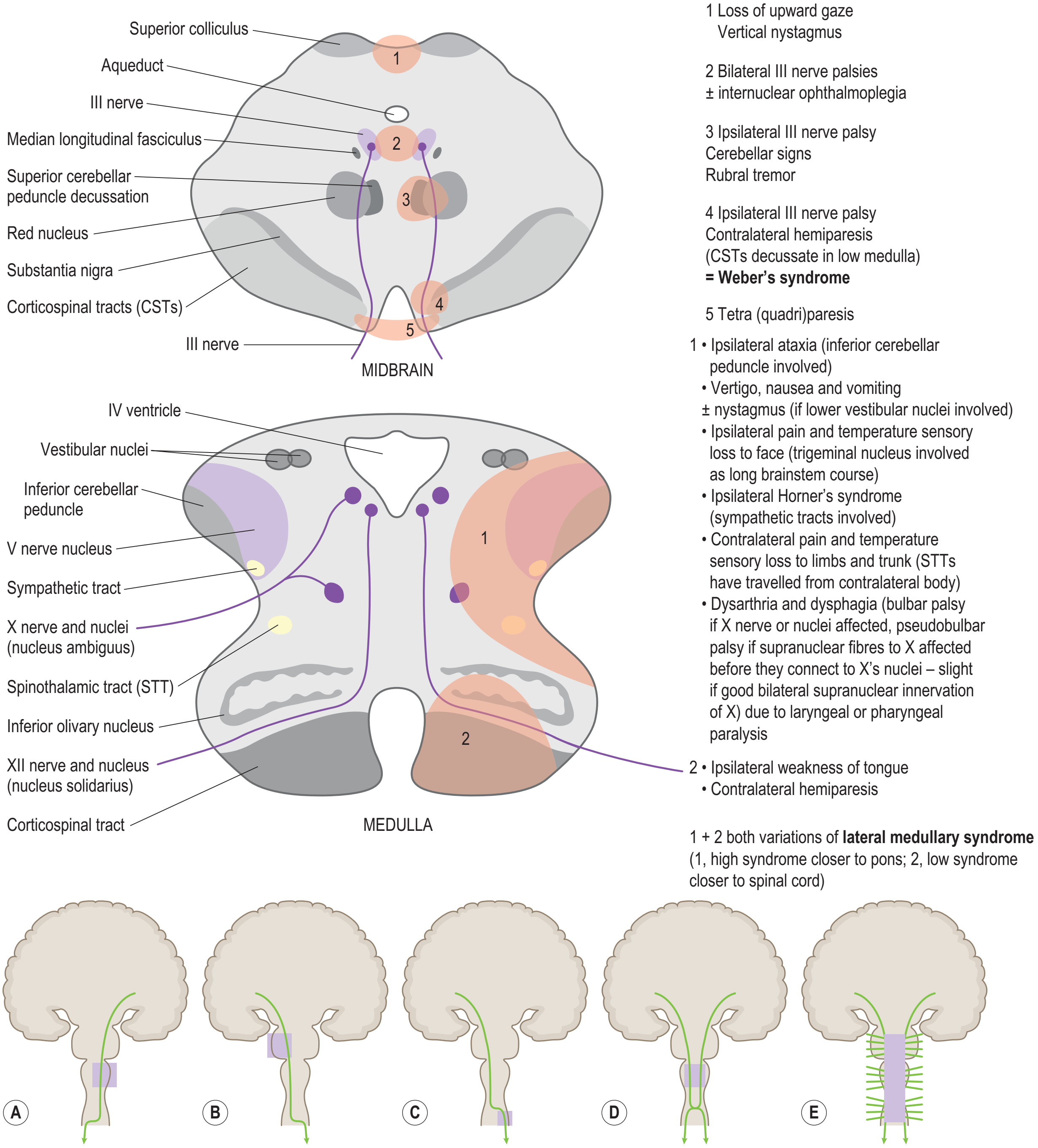
Consider function

Tell the examiners of the vital role of physiotherapists, occupational therapists and speech and language therapists in assessment and rehabilitation.

Discussion

What are some common patterns of presentation of posterior circulation strokes?

These are outlined in Table 3.39, and some examples schematically represented in Fig. 3.69 (insert). Cranial nerve


Superior colliculus
Aqueduct
III nerve
Median longitudinal fasciculus
Superior cerebellar peduncle decussation
Red nucleus
Substantia nigra
Corticospinal tracts (CSTs)
III nerve
1
2
3
4
5
MIDBRAIN
IV ventricle
Vestibular nuclei
Inferior cerebellar peduncle
V nerve nucleus
Sympathetic tract
X nerve and nuclei (nucleus ambiguus)
Spinothalamic tract (STT)
Inferior olivary nucleus
XII nerve and nucleus (nucleus solidarius)
Corticospinal tract
1
2
MEDULLA
A
B
C
D
E

1 Loss of upward gaze
Vertical nystagmus

2 Bilateral III nerve palsies
± internuclear ophthalmoplegia

3 Ipsilateral III nerve palsy
Cerebellar signs
Rubral tremor

4 Ipsilateral III nerve palsy
Contralateral hemiparesis
(CSTs decussate in low medulla)
= Weber's syndrome

5 Tetra (quadri)paresis

1
- Ipsilateral ataxia (inferior cerebellar peduncle involved)
- Vertigo, nausea and vomiting
± nystagmus (if lower vestibular nuclei involved)
- Ipsilateral pain and temperature sensory loss to face (trigeminal nucleus involved as long brainstem course)
- Ipsilateral Horner's syndrome (sympathetic tracts involved)
- Contralateral pain and temperature sensory loss to limbs and trunk (STTs have travelled from contralateral body)
- Dysarthria and dysphagia (bulbar palsy if X nerve or nuclei affected, pseudobulbar palsy if supranuclear fibres to X affected before they connect to X's nuclei – slight if good bilateral supranuclear innervation of X) due to laryngeal or pharyngeal paralysis

2
- Ipsilateral weakness of tongue
- Contralateral hemiparesis

1 + 2 both variations of **lateral medullary syndrome** (1, high syndrome closer to pons; 2, low syndrome closer to spinal cord)

Figure 3.73 Brainstem/posterior circulation stroke syndromes:
A Left cerebellopontine stroke; ataxia, right-sided weakness.
B Right Weber's syndrome; right third-nerve palsy, left-sided weakness.
C Left lateral medullary syndrome (low lateral medullary syndrome); left lower cranial neuropathies, left Horner's syndrome, left-sided weakness, (right-sided weakness if occurs above medullary decussation).
D Bilateral brainstem stroke; quadriparesis, variable cranial neuropathies, possible decreased consciousness or respiratory depression.
E Locked-in syndrome; quadriparesis, variable but classically widespread cranial neuropathies, cortex (i.e. thinking) intact.

Table 3.39 Common patterns of presentation of posterior strokes

Process	Territory of infarct	Vascular supply involved	Clinical features/examples of syndromes
Embolic or atherosclerotic	Upper brainstem Occipital lobe and visual cortex Posterior temporal and/or parietal lobe Thalamus Midbrain	Single posterior cerebral artery	Hemianopia of contralateral visual field Variable additional deficits: motor or sensory disturbance in contralateral limbs, left-sided infarct may produce reading and naming colour difficulties, right-sided infarct may produce neglect
		Bilateral posterior cerebral arteries	Bilateral visual field defects or cortical blindness
	Midbrain	Distal basilar artery	Posterior cerebral artery territories ('top of the basilar' infarct), e.g. occipital lobe and visual cortex, posterior temporal and/or parietal lobe, thalamus Midbrain territory, e.g. III nerve palsies (including Weber's syndrome – Fig. 3.73), small pupils, impaired vertical gaze
	Midbrain Pons	Basilar artery (or branches)	Bilateral signs (head/limbs) Crossed signs (ipsilateral head and contralateral limb signs), e.g. Weber's syndrome (ipsilateral III nerve palsy and contralateral limb signs) Motor and oculomotor signs predominate – corticospinal tract involvement causes limb weakness (may be bilateral) with hypertonia and hyper-reflexia; oculomotor features include diplopia, gaze palsies, nystagmus or internuclear ophthalmoplegia Facial weakness may occur Corticobulbar tracts travelling downwards may be affected with dysarthria, dysphagia and diminished gag reflex Most severe form is 'locked-in syndrome' (Case 4.35)
	Pons/cerebellum	Intracranial vertebral arteries/basilar artery (or branches)	Bilateral signs (head/limbs) Crossed signs (ipsilateral head and contralateral limb signs), e.g. Foville's syndrome (ipsilateral 'Bell's' or facial nerve palsy plus gaze palsy and contralateral hemiparesis) Sensorineural hearing loss (VIII nerve) Vertigo, nausea and vomiting (VIII nerve or pontine vestibular connections) Cerebellar signs (cerebellar stroke)
	Medulla	Intracranial vertebral arteries (or parent vertebral artery) (or branches, e.g. posterior inferior cerebellar artery)	Medullary syndromes Lateral medullary syndrome (Fig. 3.73) Variations occur depending upon slice of medulla affected, e.g. ipsilateral weakness of tongue and contralateral hemiparesis in a low medullary lesion (sometimes a medial medullary lesion); ipsilateral limb weakness in an exceptionally low lesion below the medullary decussation; weakness of one arm and the opposite leg (so-called cruciate hemiparesis) because arm and leg fibres decussate at slightly different levels; cervical radiculopathies may occur due to involvement of radicular branches of the vertebral artery
Penetrating artery disease (lacunar infarcts)	Paramedian pons	Penetrating arteries	Pure motor stroke with face, arm or leg weakness and ataxic hemiparesis
	Thalamus		Pure sensory stroke with numbness or paraesthesia of face, arm or leg Bilateral paramedian thalamus (30% of the population have a single common arterial stem supplying the medial aspect of both thalami) infarcts may provoke coma or disturbed vigilance at presentation, ophthalmoplegia, ataxia and memory impairment

Table 3.39 Common patterns of presentation of posterior strokes—cont'd

Process	Territory of infarct	Vascular supply involved	Clinical features / examples of syndromes
Dissection	Medulla Pons Any posterior circulation territory affected by emboli from dissection	Vertebral artery	Pain often a cardinal symptom, at back of neck and occiput Any posterior circulation symptoms and signs may occur (e.g. vertigo, ataxia, diplopia, limb), and these may be stepwise and multi-territory, reflecting multiple emboli emanating from the dissection
		Carotid artery	Can produce anterior circulation stroke via emboli but may also produce local compressive effects, e.g. ipsilateral Horner's syndrome due to compression of the sympathetic plexus around the carotid artery, lower cranial nerves (X and XII most obvious clinically) in the carotid sheath, VI nerve in the cavernous sinus. If ipsilateral cerebral infarction follows (due to hypoperfusion or embolisation) the clinical picture can mimic a brain stem event; in this way, carotid artery dissection can mimic vertebral artery dissection

palsies, as in Weber's and the lateral medullary syndromes described above, usually represent infarction of the nucleus or the fascicle of the nerve within the brainstem and in conjunction with associated motor and sensory signs are anatomically very helpful in localising the lesion, with the possible exception of the third-nerve nucleus which can sometimes be a false localising sign.

The following are not usually the result of posterior circulation disease:

- Isolated light-headedness, dizziness or vertigo (usually presyncope or peripheral disturbance)
- Transient decrease in consciousness (usually due to syncope or seizure)
- Drop attacks (sudden loss of postural tone and falling without warning).

What do you know about vertebral artery dissection (VAD)?

VAD is an important cause of stroke in younger people. With the advent of modern magnetic resonance (MR) imaging, it is clearly much more prevalent than previously recognised, often detected in asymptomatic people, or often with relatively limited neurological sequelae such as vertigo or isolated cranial neuropathies, although sometimes effects can be much more serious. It is much less prevalent over 50 years of age as arteries stiffen. VAD is typically provoked by minor trauma, such as neck twisting in sport, tugging at roots whilst gardening, after a minor whiplash or after spinal manipulation; even sneezing is reported as provocative. Typically within a few days thrombus that has formed in the dissected crescent may dislodge or fragment and emboli cause a posterior circulation stroke, sometimes with progressive signs as a flurry of emboli are released over time. Clinical effects may also relate to the extent of the dissection, often modest when isolated to a small section of the vertebral artery but sometimes extending into the basilar and causing luminal narrowing as well as embolic potential if the dissection is large. Carotid artery dissection may occur, but seems not to be as common as VAD. Diagnosis requires an index of suspicion, and whilst MR angiography may reveal the dissection, other MR techniques such as T1 fat subtraction imaging may reveal haematoma for months afterwards. Early anticoagulation to thwart progressive symptoms is often favoured, with a growing evidence base. Recurrence rates seem to be low.

CASE 3.32 PARKINSON'S DISEASE

Instruction

Please examine this patient's movements / upper limbs / gait and discuss your findings.

Recognition

The UK Parkinson's Disease Society brain bank clinical diagnostic criteria for diagnosing Parkinson's disease utilises a three-step approach:

Step 1 Diagnose a Parkinsonian syndrome

This requires the presence of bradykinesia + more than one of:

- *Rigidity*
- *Tremor*
- *Postural instability*:
  - *Disorder of posture* (flexion of neck and trunk)
  - *Disorder of balance* (loss of righting reflexes)
  - *Disorder of gait* (short steps, shuffling, festination, freezing).

Bradykinesia

This is essential to diagnose Parkinson's disease (Box 3.41).

Box 3.41 **Bradykinesia**

Bradykinesia refers to *slowness and progressive decrease in amplitude* of movement and is central to diagnosing Parkinson's disease. Initiating, rather than sustaining, movement, is the biggest problem.

Loss of spontaneous movement such as *diminished gesturing in conversation*, *reduced facial expression* and *reduced blinking* are often specific to Parkinson's disease, but tend to be preserved in cerebrovascular disease, a common differential diagnosis. Early signs can be subtle, and may predate diagnosis by many years.

Freezing (becoming 'glued to the spot') is a relatively late feature of Parkinson's disease.

Slowing of speech, and even *cognitive 'freezing'* are also features of Parkinson's disease.

Gait is usually affected, with *loss of arm swing*, a *stooped or forward flexed posture*, *difficulty initiating steps*, *short steps*, *shuffling* and *festination*, in which the patient appears to be chasing his or her centre of gravity. There is *difficulty turning* and *righting reflexes are reduced* (demonstrated by gently pushing your patient forwards or pulling your patient backwards, but best avoided in PACES).

Fatigability of repeated movements is impaired; *rhythmic movements*, such as stirring tea, cutting food and heeltaps, are difficult, as are *rapid alternating movements* such as touching each finger in turn with the thumb.

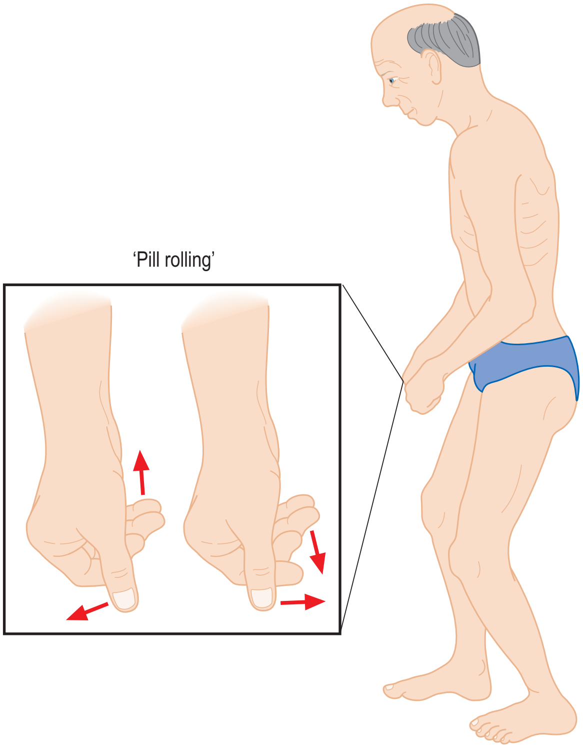


Figure 3.74 Parkinson posture and 'pill rolling'.

Rigidity

This is a *'lead pipe'* rather than 'clasp knife' resistance to passive movement with superimposed *'cogwheeling'*. The rigidity may increase if the patient is asked to perform a concurrent distracting manoeuvre in the opposite limb – *synkinesis* – such as drawing circles in the air or tapping the knee.

Tremor

This is a *low-frequency (4–6 Hz) asymmetrical 'pill rolling'* tremor most pronounced at *rest* (Fig. 3.74). An action tremor is possible in Parkinson's disease but this tends to be re-emergent rather than immediate. A *jaw or tongue tremor* is common in Parkinson's disease but a head tremor is seldom if ever a feature of Parkinson's disease and should prompt alternative diagnoses.

Step 2 Apply exclusion criteria

Exclusion criteria are listed in Box 3.42.

Box 3.42 **Exclusion criteria**

- Repeated strokes with stepwise progression
- Repeated head injury
- Antipsychotic and dopamine-depleting drugs
- Definite encephalitis and/or oculogyric crises on no drug treatment
- More than one affected relative
- Sustained remission
- Negative response to large doses of levodopa
- Strictly unilateral features after 3 years
- Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski's sign, early severe dementia with disturbances of language, memory or praxis
- Exposure to known neurotoxin
- Presence of cerebral tumour or communicating hydrocephalus

Step 3 Elicit positive supportive criteria

Supportive criteria are listed in Box 3.43.

Figure 3.75 illustrates Parkinson's disease.

Interpretation

Confirm the diagnosis

The diagnosis of Parkinson's disease is typically made at a mean age of 62–63 years, with a life expectancy of 16–17 years. Diagnosis typically takes 12–18 months, during which time various differential diagnoses of idiopathic Parkinson's disease may be considered. The overall diagnostic accuracy is around 80% in specialist clinics and 55% in general practice. Diagnosis remains clinical. 'Red flags' that should alert you to possible causes of symptoms other than Parkinson's disease are given in Box 3.44.

Parkinson's disease tends to fluctuate in severity (some days in a wheelchair, some days pushing it!) and be aware of the variable expression of Parkinson's disease.

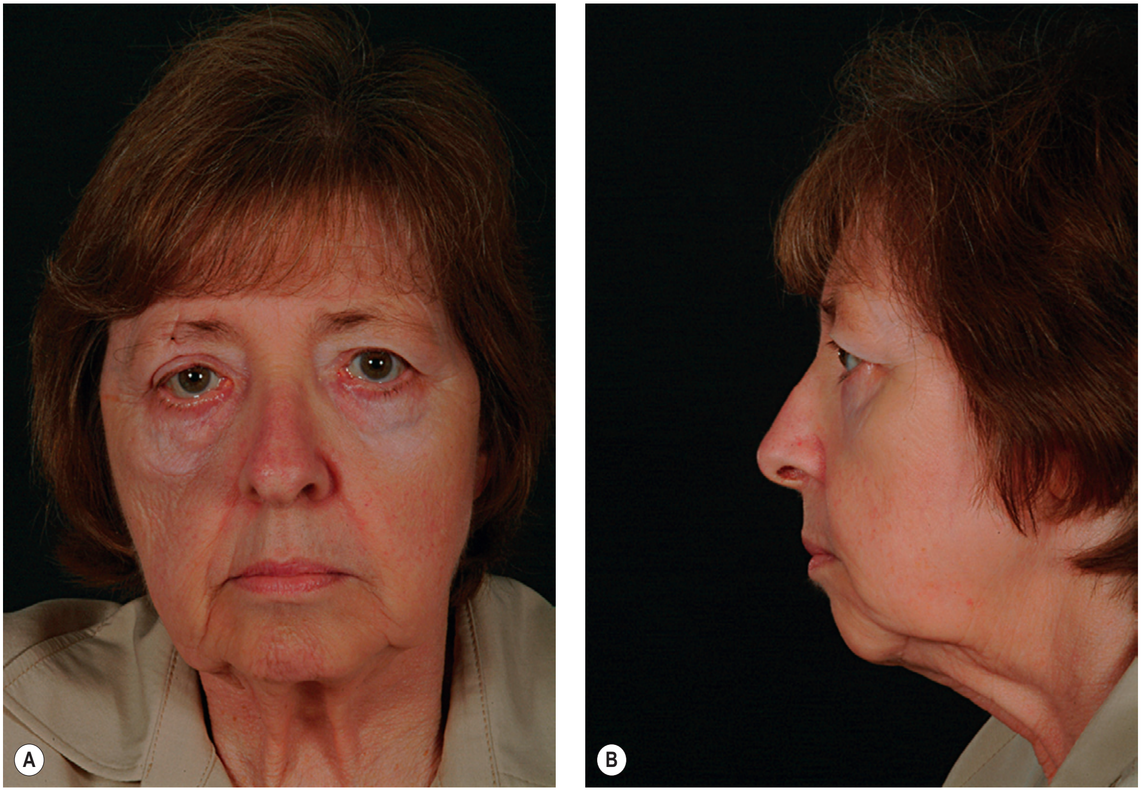


Figure 3.75 (A, B) Parkinson's disease.

Box 3.43 **Supportive criteria**

The presence of three or more of the following is required:
- Unilateral onset
- Persistent asymmetry
- Rest tremor
- Progressive symptoms
- Good response to levodopa
- Development of levodopa-induced chorea after 10 years
- Levodopa response for over 5 years
- Clinical course of over 10 years.

Box 3.44 **'Red flags'**

- Symmetry (Parkinson's disease tends to cause asymmetric symptoms)
- Lower body involvement (Parkinson's disease involves the upper body first and predominantly)
- Absent/poor response to levodopa
- Absence of long-term levodopa fluctuations or dyskinesias (these occur in most patients with Parkinson's disease after a few years)
- Early postural instability and falls (Shy–Drager syndrome)
- Early autonomic disturbance – sexual, bladder/bowel, postural hypotension (Shy–Drager syndrome)
- Early and predominant eye movement disorders (progressive supranuclear palsy)
- Early dementia (various causes)
- Early non-drug-related hallucinations (dementia with Lewy bodies)
- Early or severe dysarthria or tongue fasciculation (progressive supranuclear palsy, motor neurone disease)
- Groaning (multisystem atrophy)
- Jerks or myoclonus (multisystem atrophy)

Variations in Parkinson's disease

- Tremor-dominant Parkinson's disease is not uncommon, though it is not as common as akinetic-rigid disease or a mixture of both tremor and akinetic-rigidity.
- Postural instability is marked in some patients.
- Some patients have faster progression than expected, often with more intellectual impairment, and some have slower progression, with less intellectual impairment.

- Rare initial presentations of Parkinson's disease include involuntary extension of the great toe, and a frozen shoulder with bradykinesia and rigidity. Those with atypical early features may be mislabelled as having a 'psychogenic' cause.

What to do next – consider causes

Parkinsonism has a number of differential diagnoses other than Parkinson's disease.

Parkinsonism secondary to other causes

Secondary causes include:

- Vascular Parkinsonism
- Drug-induced Parkinsonism / toxicity (e.g. metoclopramide, prochlorperazine)
- Wilson's disease.

Some features that are more persuasive of a diagnosis of vascular Parkinsonism than idiopathic Parkinson's disease are listed in Box 3.45.

Parkinson plus syndromes

These include multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). These tend to progress more rapidly than Parkinson's disease, often leading to considerable disability within 18 months or so, and show little response to levodopa. Structural and functional neuroimaging are seldom diagnostic but in PSP there may be atrophy of the caudate nucleus, putamen, midbrain and superior cerebellar peduncle and in CBD there may be cortical atrophy and reduced cortical and striatal blood flow. MSA, PSP and CBD are outlined in Table 3.40.

Parkinsonism also occurs with other neurodegenerative disorders, e.g. dementia with Lewy bodies (Case 2.44), Alzheimer's dementia, normal pressure hydrocephalus with dementia and gait apraxia; this is not surprising because many dementias are diffuse processes and therefore disrupt extrapyramidal pathways.

Box 3.45 **Clinical features supporting vascular Parkinsonism**

- Age of onset usually later
- Risk factors for vascular disease
- Stepwise events (although unusual in practice)
- Symmetrical rigidity rather than the asymmetry of Parkinson's disease
- Lower body involvement (shuffling gait, marché a petit pas)
- Pyramidal signs possible
- No tremor

Marché a petit pas refers to a shuffling gait with small steps, more so than in Parkinson's disease, the soles of the shoes seeming to rub against the floor. Patients take tiny steps, but the feet may be slightly wider apart than in Parkinson's disease. This lower body shuffle, with relatively preserved arm swing and upper body movements, is typical of vascular Parkinsonism and body posture is upright rather than stooped; patients have a tendency to fall backwards. Vascular Parkinsonism with gait disturbance is often a precursor to a more widespread dementia that will develop over the next few years (Case 2.44 Mild cognitive impairment and dementia, Case 5.50 'Off legs' and 'collapse').

Consider severity / decompensation / complications

There are various staging and rating scales for the ongoing assessment of Parkinson's disease, including the UK Parkinson's Disease Rating Scale (UKPDRS), but this is more for use in specialist clinics. Rating scales examine both symptoms and function. The UKPDRS examines in detail:

- Mentation, mood and behaviour
- Activities of daily living (speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing, hygiene, turning in bed, falling, freezing, walking, tremor, sensory complaints)
- Motor function (speech, facial expression, tremor, rigidity, finger tapping, hand movements, rapid alternating hand movements, leg agility, arising from chair, posture, gait, postural stability, body bradykinesia)
- Complications of therapy (dyskinesias, clinical fluctuations – on / off).

It should be possible to determine whether a patient has entered the stage of complex Parkinson's disease (below).

Consider function

There are many different scales to assess activities of daily living and function in Parkinson's disease. The Northwestern University disability scale, for example, assesses five areas – walking, dressing, hygiene, eating and speech.

Discussion

Do you know of any risk factors for Parkinson's disease?

Documented risk factors include age, a non-smoking status, low caffeine intake, reduced olfaction, major depression, decreased arm swing, more than one first-degree relative affected, anhedonia, low mood, novelty-seeking personality, mental inflexibility and alcoholism. However, some of these, such as reduced olfaction and reduced arm swing, are more likely early features of disease. Others are not convincingly associated.

What causes Parkinson's disease?

Parkinson's disease has a prevalence of 1% at > 65 years rising to 2% by > 80 years. The cause is unknown, but a proportion of patients have an identifiable genetic predisposition (α-synuclein). In most, there is no family history, although the evidence for genetic roles is increasing, with an increasing number of 'PARK' genes being characterised. Many environmental causes have been postulated but most of these probably induce a Parkinsonian syndrome rather than being causative for Parkinson's disease.

Table 3.40 Parkinson plus disorders

	Frequency	Age group	Pathology	Clinical features
Multiple system atrophy (MSA)	The largest of the Parkinson plus group	Mean age of onset 54 years	Glial cytoplasmic inclusions (GCIs)	A combination of Parkinsonism, cerebellar features and autonomic dysfunction (also corticospinal tract signs with brisk reflexes common, dyskinesia common, dementia rare): The Parkinsonism requires, typically, bradykinesia plus one of rigidity, tremor or postural instability. Tremor occurs in two-thirds of patients and is seldom pill-rolling and more often irregular, jerky, myoclonic and both postural and with action. The cerebellar features include gait ataxia and ataxic dysarthria. The autonomic features include falls due to orthostatic hypotension, bladder dysfunction (incontinence or incomplete emptying) and sexual dysfunction. Those with predominantly Parkinsonism are designated as having the MSA-P subtype (formerly striatonigral degeneration) and those with predominantly cerebellar features the MSA-C subtype (formerly olivopontocerebellar atrophy). MSA-P is more common than MSA-C. A predominantly autonomic presentation of MSA (formerly Shy–Drager syndrome) may be confused with pure autonomic failure, which has a Lewy body basis.
Progressive supranuclear palsy (PSP)	PSP is not rare	Median age of onset 60–65 years	Neurofibrillary tangles, neurophil threads and tau tufts in basal ganglia and brainstem	Vertical supranuclear gaze palsy, with loss of downward gaze, characteristic An early tendency to falls and postural instability Symmetrical bradykinesia and axial rigidity Pseudobulbar dysarthria Mild dementia
Corticobasal degeneration (CBD)	CBD is a less common cause of symmetrical Parkinsonism in which there are additional cortical signs	Symptoms usually start after 60 years		An early clumsy limb, often a rigid arm, characteristic (rigidity much more marked than in Parkinson's disease). The arm later becomes useless, often with focal myoclonus. Cognitive impairment within 1–3 years with dyspraxia (patients often complain that their arm does not understand tasks), cortical sensory loss and memory loss. Sometimes so-called 'alien limb syndrome' occurs in which a limb appears to the patient to have a life of its own (e.g. if scratching, a patient will deny that it is their own hand doing the scratching). Progressive gait disturbance, dystonia, dysphagia, dysarthria and corticospinal tract signs.

What is the pathology in Parkinson's disease?

The pathology is degeneration of dopaminergic pathways with a depigmented substantia nigra, and the presence of cytoplasmic inclusions called Lewy bodies. Lewy bodies may also occur diffusely and give rise to dementia with Lewy bodies. Lewy bodies may also cause rapid eye movement sleep disturbance or autonomic disturbance. A few Lewy bodies can be a normal finding.

What is essential tremor?

This is a bilateral postural tremor (action, kinetic) but there can be a resting component. It is increasingly not viewed as a monosymptomatic disorder but as a neurodegenerative disorder that can produce cerebellar and gait problems. Half are alcohol responsive. It may be familial, but there is increasing evidence for environmental toxins, such as harmines, which are products of burnt food. Essential tremor is discussed in Case 2.19.

Is there a role for neuroimaging in Parkinsonism?

Computed tomography (CT) can be useful in excluding other conditions, such as cerebrovascular disease, and normal pressure hydrocephalus in patients with an early gait disorder. Magnetic resonance imaging (MRI) can sometimes be useful if MSA or PSP is suspected but there is poor sensitivity for the changes suggesting these conditions. Functional imaging with single photon emission computed tomography (SPECT) uses the tracer FP-Cit, otherwise known as a DaT scan. The tracer binds to dopamine transporters on presynaptic dopaminergic neurons and gives an indirect measure of dopaminergic function. It may be used to distinguish Parkinson's disease from essential tremor; in the latter the scan is normal but in Parkinson's disease loss of the 'tail of the comma' is seen bilaterally, representing putaminal degeneration. A DaT scan is capable of distinguishing these two conditions with 97–98% sensitivity and specificity. It cannot reliably distinguish Parkinson's disease from other Parkinsonian syndromes, since it only evaluates integrity of the nigrostriatal pathway, which is affected in all Parkinsonian syndromes, although neuron loss is more likely to be asymmetrical in Parkinson's disease. Interestingly, an increasingly recognised clinical method of distinguishing essential tremor from a Parkinsonian tremor is the thumb extension component in essential tremor to what may otherwise look like a typical Parkinsonian tremor.

What do you know about non-motor symptoms in Parkinson's disease?

Many neurotransmitters are disrupted in Parkinson's disease, and the diverse array of structures involved, and therefore symptoms, is increasingly appreciated. They are summarised in Table 3.41.

What are the stages of Parkinson's disease?

Parkinson's disease is a progressive disease requiring a multidisciplinary team approach. It is helpful to consider the four management stages proposed by MacMahon and utilised in National Institute for Health and Clinical Excellence (NICE) guidelines:

- Diagnosis
- Maintenance treatment
- Complex disease
- Palliative care.

Diagnosis is around 18 months, usually with observation. It is usually important not to plunge into treatment quickly before getting an idea of the individual pattern of disease. Treatment should always be individualised. Once treatment is started, it is seldom stopped, and most patients receive maintenance treatment for around 5 years before entering the complex stage. Complex may mean more than two drugs or more than four doses or frequent drug changes or side effects. Patients in the complex stage generally attend Parkinson's disease or movement disorder clinics, where they may benefit additionally from multidisciplinary care, e.g. physiotherapists to help with gait and postural instability and activities of daily living, speech and language therapists to assist with speech and swallowing and occupational therapists to assess the need for domiciliary adjuncts. If a patient survives long enough, the priority may no longer be to increase drug doses but to maintain dignity. Important issues may include managing dementia, managing drug-induced psychiatric side effects and appropriate reduction in pharmacotherapy.

What are the treatments in Parkinson's disease?

Broadly, the treatments for the motor symptoms centre on dopamine replacement and fall into three categories (Box 3.46).

When should treatment in Parkinson's disease be started, and what agent should be used?

An optimum time to start treatment remains unclear, as does the best starting drug. Generally levodopa is used in older people, or those with comorbidity, and a non-ergot dopamine agonist in those who are younger and otherwise well. Enzyme inhibitors are generally add-on agents to levodopa.

The TEMPO trial with rasagiline (not compared with any other drug) was a delayed start trial, and the first of several ongoing trials as well as the PD Med trial on early treatment. The ADAGIO study demonstrated significant longer term improvement in those who commenced rasagiline at entry compared with those who started treatment later. However, the notion of any drug being neuroprotective is still without a clear evidence base, and further head-to-head studies of different agents as monotherapy in early disease are needed, although the use of a monoamine oxidase-B inhibitor in early disease is favoured by some because of the relative convenience of a once-daily drug and relatively few side effects.

What impulse control disorders do you know of in Parkinson's disease?

These include gambling, hypersexuality and compulsive eating or shopping. Punding refers to perseverative behaviours such as removing clothes from the wardrobe and refolding them neatly, returning them to their usual place, and then doing this all over again; and sometimes again, and again, and again. Excessive hobby-ism, such as playing computerised chess, is also common. Dull, but there you have it. All of these are associated with aberrant or excess stimulation of dopaminergic reward systems, and with loss of control, continued engagement in such activities despite adverse psychological, social or financial consequences, and withdrawal resulting in craving. They are associated particularly, but not exclusively, with dopamine agonists. Dopamine dysregulation syndrome refers to compulsive use of escalating doses of levodopa despite adequate motor control (akin to substance addiction),

Table 3.41 Non-motor symptoms and strategies in Parkinson's disease

Neuropsychiatric symptoms	Depression / anxiety	Selective serotonin reuptake inhibitors (not with selegiline) Tricyclic antidepressants (anticholinergic side effects) Cognitive behavioural therapy
	Hallucinations / dementia	Review anti-Parkinsonian medication Cholinesterase inhibitors, e.g. rivastigmine Psychiatric support
Sleep disorders	Restless leg syndrome	Low-dose dopaminergic therapy
	Nocturnal akinesia	Modified release levodopa
	Periodic limb movements	
	Insomnia	
	Vivid dreams	Review anti-Parkinsonian medication
	Rapid eye movement sleep behaviour disturbance	Clonazepam
	Daytime somnolence	Modafinil
	Sudden sleep attack	
Autonomic symptoms	Bladder disturbance (urgency, nocturia, frequency)	
	Sweating	
	Sialorrhoea	Encourage swallowing of saliva Speech and language therapy 1% sublingual atropine ophthalmic solution Salivary gland botox injection or radiation
	Sexual dysfunction (hypersexuality / erectile dysfunction)	Beware dopamine agonists Avoid alpha blockers Erectile dysfunction therapies
	Orthostatic hypotension	Modify medication Elevate head of bed Encourage fluid and salt intake Fludrocortisone / midodrine
Gastrointestinal symptoms	Dysphagia	Speech and language therapy Videofluoroscopy dietitian Enteral or percutaneous gastrostomy feeding
	Choking	
	Weight loss	
	Nausea and vomiting	
	Constipation	Adequate fluid intake / diet / exercise Laxatives / enemas
	Faecal incontinence	
Sensory symptoms	Pain	
	Paraesthesia	
	Olfactory loss	
	Blurred vision	
Other	Falls	Multifactorial assessment
	Fatigue	

Box 3.46 **Strategies for treating motor symptoms in Parkinson's disease**

Aims of treatment

Currently there is not a cure for Parkinson's disease and the aim of drug treatment is to control symptoms and so improve function and quality of life. It is seldom possible to abolish symptoms, and treatment is often a trade-off between improving one symptom and potentially inducing a drug side effect. There is no evidence that any drug improves prognosis but the concepts of neuroprotection, which would ideally start before symptoms, and neurorestoration remain unresolved.

Types of treatment

There are three strategies to treating motor symptoms, all the results of dopamine depletion – replacing dopamine with levodopa (LD), enhancing the effects of dopamine with dopamine agonists or reducing dopamine breakdown with enzyme inhibitors. The ongoing PD Med trial aims to determine which drugs might be favourable as initial treatment and how best to escalate treatment. However, the best strategy is likely to remain individually determined.

Dopamine LD

LD is the most potent drug for Parkinson's disease and is the mainstay of therapy. It is generally used as first-line treatment in patients with comorbidity or cognitive impairment. Essentially all new patients with Parkinson's disease respond. Preparations are Sinemet or Madopar in various doses; both contain a peripheral decarboxylase inhibitor. LD can reduce disability and prolong activities of daily living, but it does not stop disease progression. The side effects of LD are postural hypotension, cognitive disturbance, dyskinesias and on–off phenomena (sudden, unpredictable fluctuations between bradykinesia or freezing and LD-induced dyskinesia). The problem with dyskinesias is progressively more likely with time and it seems preferable to limit LD dosage to a maximum of 500 mg daily. Dyskinesias generally do not develop for a few years.

Dopamine agonists (DAs)

A DA may be considered as initial therapy if there is no comorbidity and no cognitive impairment and the patient has a considerable life expectancy; they are sometimes considered as adjuvant therapy, but neuropsychiatric side effects may limit their use. DAs provide enhanced 'background' levels of dopamine, which may be sufficient to help patients with mild disease or, as add-in therapy, to help smoothen the effects of LD or spare high LD doses. DAs may be ergot derived (cabergoline, bromocriptine, lisuride, pergolide) but these carry a risk of pulmonary fibrosis, retroperitoneal fibrosis and pleural effusions; in practice, therefore, non-ergot DAs (ropinirole, pramipexole, and rotigotine available as a patch), which do not carry the same side effect profile (although there are concerns about gambling, punding and hypersexuality), are now almost always prescribed in new patients. Whilst DAs seem to be useful in reducing motor complications, this benefit may be outweighed by non-motor side effects.

Enzyme inhibitors reducing dopamine breakdown

Catechol-*O*-methyl transferase (COMT) inhibitors may be especially useful if there is a wearing-off effect before the next dose of LD is due. However, they may also have a place at any stage of the disease. Entacapone is the main COMT inhibitor, but tolcapone has recently been reintroduced after being withdrawn because of a small but important risk of serious liver disease. Monoamine oxidase (MAO)-B inhibitors (selegiline and second-generation MAO-B inhibitor rasagiline) are also used.

Current common treatment regimens

Primary treatment is usually been with LD or a DA. Add-in treatment is then often as follows:

- DA + LD + COMT inhibitor or
- LD + COMT inhibitor + DA.

However, some now favour the use of MAO-B monotherapy in early disease.

Other treatments

Apomorphine is a potent DA that is used in advanced disease subcutaneously. Duodopa is a concentrated suspension or gel that is infused into the duodenum via a portable pump through a percutaneous endoscopic gastrostomy tube; it can produce smoother plasma levels than LD, and increase the 'on' time without severe dyskinesias. Anticholinergics may be used for tremor, but side effects (confusion, constipation, blurred vision, dry mouth) are seldom worth the price. Amantadine was introduced historically as a treatment for Parkinson's disease but is relatively ineffective; it has, however, re-emerged as a treatment for LD-induced dyskinesias in some patients. Surgery is occasionally considered.

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and may occur in isolation or be associated with impulse control disorders. Although now notorious, most patients do not experience impulse control problems and it may be that some who do have underlying dopamine receptor polymorphisms. Treatment is without an evidence base, although reduction, withdrawal or switching of dopamine agonist seems a sensible measure.

Why do patients with Parkinson's disease develop complications after a period of time on levodopa, and what are these complications?

Dopamine release is not continuous in normal brains, with background basal release and bursts on top, but these are not as dramatic as the swings after a few years of levodopa. Levodopa causes dopamine levels in the brain to swing up and down, leading to changes in phosphorylation and activation of receptors, particularly glutamate receptors, so that the basal ganglia fire in bursts rather than smoothly with non-physiological stimulation of postsynaptic dopamine receptors. This results in breakthrough periods of involuntary movements (dyskinesias) and wearing 'off' periods. Other factors such as disease duration and levodopa dosage are important.

Why is there a period of smooth control before wearing off develops?

The brain is probably able to buffer for a while, surviving neurons able to take up levodopa, metabolise it to dopamine and release it. It may be that in time less neurons are able to do this and non-dopaminergic neurons also take up levodopa and release it more chaotically.

When do patients treated with levodopa start to show signs of wearing off?

Half of all patients show signs within 5 years. The timescale depends upon the patient, and younger patients with a genetic basis may develop motor complications within a year or two. Older patients seem less prone to the motor symptoms of dyskinesias and wearing off, but more prone to non-motor complications including cognitive impairment. This said, wearing off is probably under-recognised, especially in older people, and especially in those in care homes.

What are the signs of wearing off?

Early signs of wearing off may be very subtle, whilst later signs are overt, with dramatic and unpredictable on–off phases.

How may wearing off be minimised or prevented?

Longer acting levodopa preparations may have a role, with continuous dopaminergic stimulation. Some experts recommend combination therapy early in disease, providing 24-hour dopaminergic stimulation. Neuroprotective drug strategies theoretically should prevent dyskinesias and wearing off. None of these strategies are evidence based. The ELLDOPA study showed that higher daily doses of levodopa (600 mg) significantly increase the risk of dyskinesia, hypertonia, headache, nausea and infection. Adjuvant therapies should probably be considered at levodopa doses of around 400 mg daily.

How may wearing-off symptoms be managed?

The most effective strategies to reduce motor fluctuations are probably deep brain stimulation of the subthalamic nucleus (STN-DBS), levodopa infusions, and apomorphine. Careful surveillance is needed from when patients are entering this new, more complex stage of illness. The aim is for smooth control of symptoms, but simply increasing the dose of levodopa will bring with it an inherent risk of dyskinesias, and levodopa-sparing therapies should probably be considered when patients are still in the maintenance phase of disease. In cognitive impairment and those without healthy looking MRI, STN-DBS poses greater surgical complications. DBS of the internal pallidum (GPi) may pose lower risk. Surgery may improve dopa-responsive symptoms, and will not improve patients beyond their best response to levodopa, except in a small number of patients with levodopa refractory tremor that can be helped by thalamic or subthalamic DBS (or gamma knife thalotomy in those at high risk of surgery).

Which therapies are recommended for first-line adjuvant treatment?

The NICE guidelines allow most things. It is all about tailoring treatment to the individual, and sharing several drug options, with surgical therapies always in the back of the mind. Most dopaminergic drugs, like levodopa, can cause postural hypotension, confusion, hallucinations and nausea.

Catechol-O-methyl transferase (COMT) inhibitors

Entacapone must be given with each dose of levodopa, often as a combined preparation (Stalevo). It prolongs the action of levodopa, although some think this is only by half an hour to an hour or so. It is not always very effective, but this may reflect ineffective taking. Diarrhoea is a side effect.

MAO-B inhibitors

Selegiline and rasagiline are convenient as once-daily doses. The LARGO study showed that rasagiline reduces mean daily off-time and improves symptoms in levodopa-treated patients with motor fluctuations, an effect similar to entacapone. The LARGO-Ancillary Study showed that rasagiline also improved motor performance during the off period before the first morning dose of levodopa, probably because it has continuous clinical effect throughout the day and night from a once-daily dose. Rasagiline is generally well tolerated. Selegiline may be more likely to cause postural hypotension, confusion and hallucinations, but some say rasagiline is only better tolerated because it is less effective. Others are firm supporters of rasagiline and anecdotal evidence suggests it also improves gait and freezing disorders. Rasagiline appears to be gaining predominance.

Dopamine agonists

These are generally less well tolerated as adjuvant therapy in older people and should be avoided in confusion and dementia, which are exacerbated by these drugs.

Deep brain stimulation, continuous levodopa (Duodopa) and apomorphine

Deep brain stimulation is generally considered before Duodopa gel. Apomorphine can be very effective.

How may morning motor function problems be tackled?

Dispersible levodopa can be used before a patient gets out of bed. A COMT inhibitor at night does not seem to be as useful as a MAO-B inhibitor. Some would use controlled-release levodopa. Some would use a dopamine agonist, but sleep disturbance is common. Some would consider surgery when off periods in the morning start to become very troublesome.

What do you know about the patient perspective in Parkinson's disease?

Parkinson's disease is a condition in which individualised care is vital, and patients should be engaged in day-to-day management. Unmet needs are common, impacting on day-to-day care, and a Parkinson's Disease Society survey, Life with Parkinson's Today – Room for Improvement, the largest survey of its type, found many people were not given clear information on diagnosis and treatment. Furthermore, many patients are still not referred for specialist assessment, despite NICE guidance that all need specialist input.

What do you know about dementia in Parkinson's disease?

Parkinson's disease dementia (PDD) affects the vast majority of people with Parkinson's disease at 20 years and is distinguished from dementia with Lewy bodies by its time of onset. Both PDD and dementia with Lewy bodies have the pathological hallmark of Lewy bodies, but in PDD Lewy bodies progress subcortically to cortically from a Parkinson's disease background whereas in dementia with Lewy bodies they progress cortically to subcortically to produce early cognitive impairment and later Parkinsonism.

What do you know about palliation in Parkinson's disease?

Many patients in care homes have Parkinson's disease, and these patients must have access to high-quality end-of-life care. It should be recognised that at all stages Parkinson's disease warrants symptom control and palliation, and the value of the array of therapists and specialist nurses is paramount.

CASE 3.33 CEREBELLAR DISEASE

Instruction

Please examine this patient's speech and upper limbs and discuss your findings.

Recognition

There is slurred speech dysarthria. There is *upper limb ataxia with an action tremor, inability to judge distance (dysmetria) with past pointing* and *dysdiadochokinesis*.

Interpretation

Confirm the diagnosis

Tell the examiners that you would examine for nystagmus and for heel–shin ataxia and for a wide-based gait.

What to do next – consider causes

Unilateral cerebellar disease causes ipsilateral signs. Midline (vermis) lesions cause midline or truncal ataxia. Cerebellar hemisphere lesions cause appendicular or limb ataxia. These principles may suggest whether cerebellar pathology is unilateral or bilateral, midline, hemispheric or pancerebellar. This should narrow the differential diagnosis to structural lesions or more generalised insults. Causes of cerebellar disturbance are shown in Figure 3.76.

Consider severity / decompensation / complications

This depends upon the underlying cause.

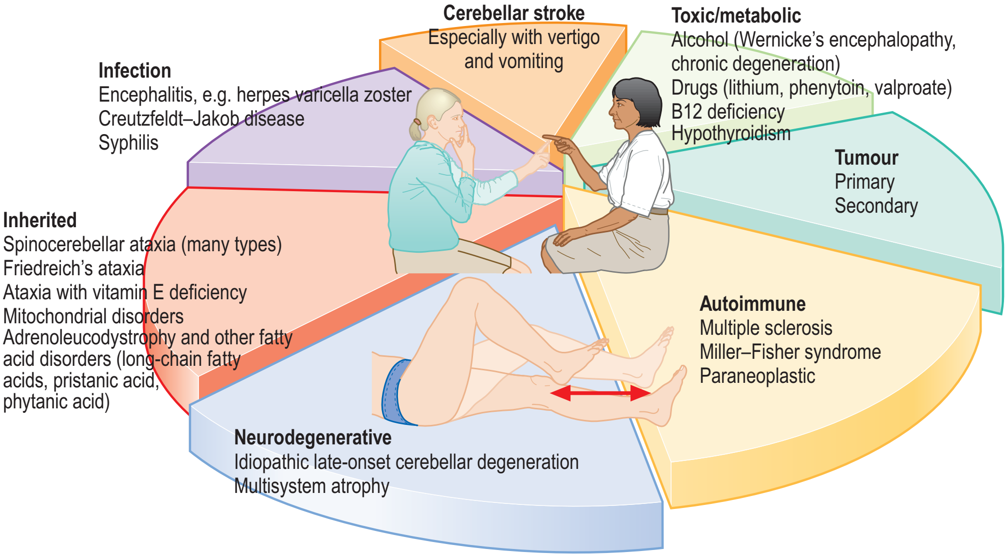

Cerebellar stroke
Especially with vertigo and vomiting
Toxic/metabolic
Alcohol (Wernicke's encephalopathy, chronic degeneration)
Drugs (lithium, phenytoin, valproate)
B12 deficiency
Hypothyroidism
Infection
Encephalitis, e.g. herpes varicella zoster
Creutzfeldt–Jakob disease
Syphilis
Tumour
Primary
Secondary
Inherited
Spinocerebellar ataxia (many types)
Friedreich's ataxia
Ataxia with vitamin E deficiency
Mitochondrial disorders
Adrenoleucodystrophy and other fatty acid disorders (long-chain fatty acids, pristanic acid, phytanic acid)
Autoimmune
Multiple sclerosis
Miller–Fisher syndrome
Paraneoplastic
Neurodegenerative
Idiopathic late-onset cerebellar degeneration
Multisystem atrophy

Figure 3.76 Cerebellar ataxia.

Consider function

Tell the examiners that you would like to assess gait and falls risk.

Discussion

Does cerebellar disturbance cause vertigo?

Unwary physicians should remember that cerebellar disturbance causes incoordination of movement. Vertigo is a result of disturbance in the vestibular system, either peripherally in the vestibular nerve (a division of the eighth cranial nerve which also provides the division for hearing) and its system of semi-circular canals, or in the brainstem connections to the vestibular nerve located in the pons. Thus a pathological process involving the cerebellopontine angle may cause both incoordination and vertigo but a pure cerebellar problem will not cause vertigo. Different types of nystagmus may of course occur in cerebellar disease, brainstem disease or indeed vestibular disease (Case 3.19 Nystagmus).

CASE 3.34 SPASTIC PARAPARESIS AND BROWN–SÉQUARD SYNDROME

Instruction

Please examine this patient's lower limbs and discuss your findings.

Recognition

Spastic paraparesis

There is *weakness, increased tone and clonus in both legs* with *enhanced reflexes* and *extensor plantar responses* – an upper motor neuron pattern of weakness. There may be signs of radiculopathy at the level of the lesion.

Brown–Séquard syndrome

There is *spastic weakness* (monoplegia – one limb, or hemiplegia – arm and leg), with *enhanced reflexes* and *loss of proprioception and vibration sense* on one side (ipsilateral to the lesion), and *loss of pain and temperature sensation* on the other (contralateral to the lesion). There may also be ipsilateral root signs at the level of the lesion.

Spastic paraparesis and Brown–Séquard syndrome are illustrated in Figure 3.77.

Interpretation

Confirm the diagnosis

Confirm spastic paraparesis (lower limbs only) and not tetraparesis (four limbs). Tetraparesis implies a lesion above C4. Try to seek a sensory level. True Brown–Séquard syndromes, with 50% hemisection, are rare; usually lesions are more or less than one wing of the butterfly that is spastic paraparesis and a spastic paraparesis can be markedly asymmetrical.

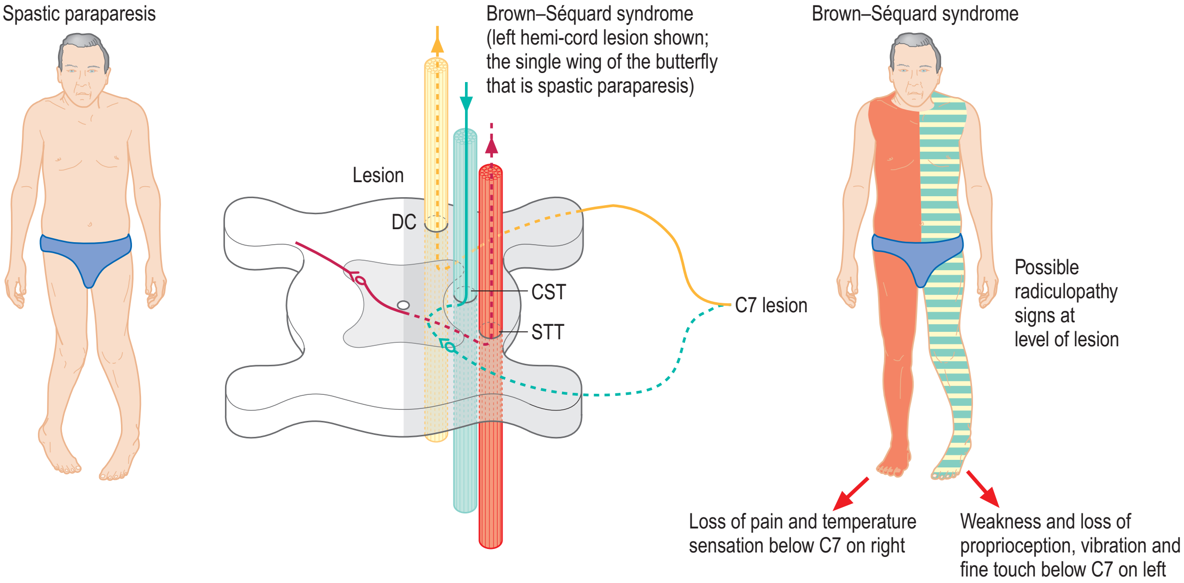

Spastic paraparesis
Brown–Séquard syndrome (left hemi-cord lesion shown; the single wing of the butterfly that is spastic paraparesis)
Lesion
DC
CST
STT
C7 lesion
Brown–Séquard syndrome
Possible radiculopathy signs at level of lesion
Loss of pain and temperature sensation below C7 on right
Weakness and loss of proprioception, vibration and fine touch below C7 on left

Figure 3.77 Spastic paraparesis and Brown–Séquard syndrome. CST, corticospinal tracts; DC, dorsal columns; STT, spinothalamic tracts.

What to do next – consider causes and assess other systems

An *anterior cord syndrome* refers to complete motor paralysis (corticospinal tracts) and sensory anaesthesia (spinothalamic tracts). *Brown–Séquard syndrome* is an *incomplete* cord syndrome. A *central cord syndrome* is typically due to an extension injury to an osteoarthritic spine; the central grey matter is mostly affected and motor loss tends to be greater in the arms than the legs (fibres to the lower body are more peripheral) with variable sensory sparing. Cord lesions may be non-compressive or compressive.

Lesions which can appear to be spinal because of tetraplegia but are not include bilateral cortical lesions, parasagittal meningiomas and syringomyelia / bulbia.

Non-compressive spinal cord disorders

These are outlined in Table 3.42.

Compressive spinal cord disorders

Extradural lesions include cervical spondylosis (myelopathy or radiculopathy), cervical / lumbar disc prolapse, tumours and trauma. Intradural lesions may be intramedullary such as meningiomas or neurofibromas or extramedullary such as astrocytomas.

Consider severity / decompensation / complications

Tell the examiners that you would ask about sphincter disturbance (bladder or bowel symptoms, urinary catheter) and initially exclude acute cord compression, a neurosurgical emergency.

Consider function

Tell the examiners you would determine the level of disability and, as well as identifying and correcting any correctable cause, work closely with physiotherapy and occupational therapy colleagues to optimise function.

Discussion

How does the blood supply to the spinal cord influence clinical features of infarction?

The anterior cord is supplied by the anterior spinal artery, artery of Adamkiewicz, a radicular artery that contributes significantly to the lower thoracic and lumbar cord and multiple radicular arteries. The posterior cord is supplied by the posterior spinal arteries supplemented by posterior radicular arteries. Infarction may occur in watershed areas between the anterior and posterior systems, e.g. after cardiac arrest. The dorsal columns are invariably preserved, with normal proprioception and sensation of vibration and light touch.

What is the prognosis for recovery in spinal cord infarction?

This is generally poor if there is no improvement in the first 48 hours.

Where do spinal arteriovenous malformations (AVMs) tend to occur?

Dural AVMs are mostly thoracolumbar, and lie in the spinal dura and nerve roots, supplied by branches of the intercostals and lumbar arteries.

What is spinal muscular atrophy?

This is the second commonest hereditary neuromuscular disorder after Duchene muscular atrophy (1 in 25 000 live births). It has many forms, localised to the *SMN* gene on chromosome 5, which has a role in RNA processing. Spinal muscular atrophy is classified according to age (childhood or adult), distribution (proximal, distal, bulbar) and mode of inheritance (dominant, recessive, X-linked).

What is hereditary spastic paraparesis?

This is a typically, but not exclusively, an X-linked recessive disease developing at any age with difficulty walking. Paradoxically, the earlier the presentation the milder is the disease. The spastin gene is one of numerous that can be at fault.

Is myelopathy common in human immunodeficiency virus (HIV)?

It occurs clinically in 7% of patients and at post-mortem in 50%, and may be vacuolar or multinucleate giant cell, the former more common and a marker of late disease (CD4 count < 200 / μl). The mechanism is uncertain and may involve microglial neurotoxicity, gp120 protein myelin toxicity or B12 deficiency. There is no treatment. Myelitis may occur at seroconversion. Human T-cell lymphotropic virus type 1 (HTLV-1), endemic in parts of the world, is transmitted similarly to HIV and may cause insidious spastic paraparesis, peripheral neuropathy, ataxia or optic atrophy. HIV may also cause myelitis via a range of opportunistic infections, usually with marked immunosuppression.

What investigations might you consider when investigating a spinal cord syndrome?

These include magnetic resonance imaging (MRI), cerebrospinal fluid examination for microscopy and culture, protein, glucose, oligoclonal bands and polymerase chain reaction testing (for viruses), electrophysiology, erythrocyte sedimentation rate and autoimmune profile, B12, viral serology and syphilis serology (if suspicion).

How might MRI further the diagnosis?

It can exclude cord compression and sometimes identify signal change consistent with myelitis. Cord atrophy is possible in neurodegenerative and nutritional causes, and signal change may occur in subacute combined

Table 3.42 Non-compressive spinal cord disorders

	Causes	Clinical clues
Acute transverse myelopathy Acute weakness Sensory level Bilateral Sometimes asymmetrical	Multiple sclerosis	Transverse myelitis or partial cord syndrome
	Viral (e.g. varicella zoster virus, herpes simplex virus, cytomegalovirus)	Radicular pain at onset (can also occur in compressive lesions) Plateau phase for several months Partial recovery Residual disability 30%
	HIV infection	May be none – acute seroconversion myelitis
	Autoimmune	e.g. systemic lupus erythematosus
Vascular	Infarction	Sudden painful flaccid paraparesis Urinary retention Later spasticity and hyper-reflexia Normal proprioception, vibration and light touch
	Haemorrhage	Similar to infarction
	Arteriovenous malformation	Slowly evolving mixed upper and lower motor neuron signs Sensory disturbance Sometimes sphincter disturbance
Infective	HIV myelitis	Acute seroconversion myelitis Slowly progressive spastic paraparesis and sensory ataxia in late disease Opportunistic infection myelitis (varicella zoster virus, cytomegalovirus, syphilis, tuberculous)
	Syphilis	Absent ankle jerks and extensor plantars
	Tuberculous myelitis	History of or risk factors for tuberculosis, or HIV
	Lyme disease	Radiculoneuromyelitis involving lower and upper motor neurons Resembles amyotrophic lateral sclerosis
	West Nile virus	Acute, asymmetrical flaccid weakness due to anterior horn cell involvement
Hereditary/degenerative	Friedreich's ataxia	Absent ankle jerks and extensor plantars
	Spinal muscular atrophy	Progressive weakness and wasting and hypotonia due to degeneration of anterior horn cells or bulbar motor nuclei Differential diagnosis of motor neurone disease
	Hereditary spastic paraparesis	Spasticity Hyper-reflexia and extensor plantars Weakness less striking Mild sensory symptoms Mild pes cavus possible
	Rare causes, e.g. abetalipoproteinaemia, X-linked adrenoleucodystrophy	
Motor neurone disease	Amyotrophic lateral sclerosis	
Nutritional	Subacute combined degeneration of cord	Absent ankle jerks and extensor plantars
	Vitamin E deficiency	
Toxic	e.g. lathyrism, konzo, tropical ataxic neuropathy	Endemic in some parts of the world

HIV, human immunodeficiency virus.

Box 3.47 **Treatments for myelopathy**

- Surgical decompression
- Intravenous aciclovir 10 mg/kg 8-hourly for suspected or confirmed herpes simplex myelitis
- Pulsed methylprednisolone 0.5–1 mg daily for 3 days for suspected multiple sclerosis
- Vitamin B12 replacement as hydroxocobalamin 1000 μg daily for 5 days then monthly
- Antiretroviral therapy to prevent vacuolar myelopathy
- Symptom control, e.g. pain
- Rehabilitation

degeneration of the cord. Cord infarction or inflammation may appear as high signal on T2-weighted scans, sometimes associated with focal cord swelling.

What treatments are there for myelopathy?

Treatments are outlined in Box 3.47.

CASE 3.35 SYRINGOMYELIA

Instruction

Please examine this patient's arms neurologically. He has a history of altered pain sensation.

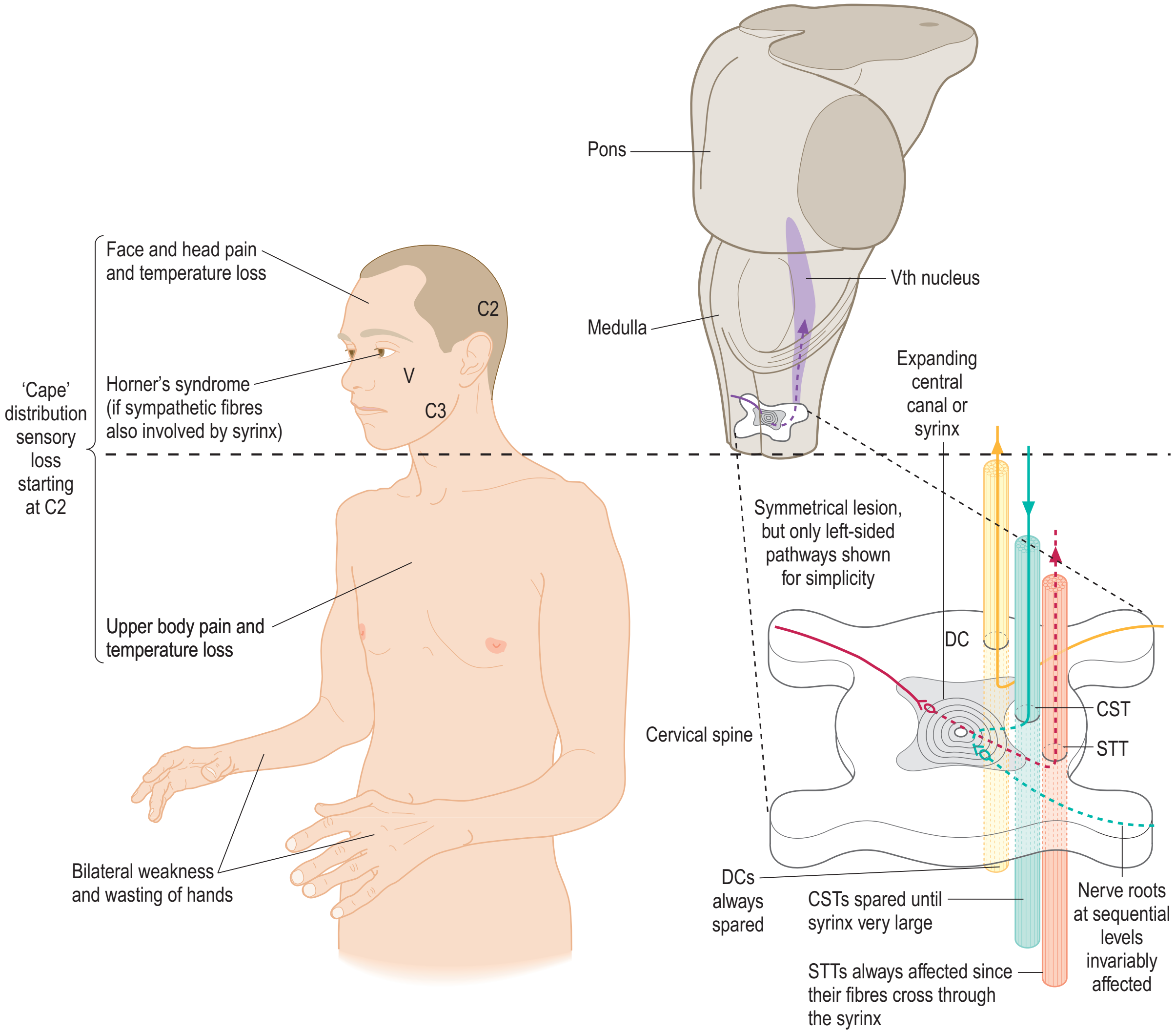

Face and head pain and temperature loss
'Cape' distribution sensory loss starting at C2
Horner's syndrome (if sympathetic fibres also involved by syrinx)
Upper body pain and temperature loss
Bilateral weakness and wasting of hands
C2
V
C3
Pons
Medulla
Vth nucleus
Expanding central canal or syrinx
Symmetrical lesion, but only left-sided pathways shown for simplicity
DC
Cervical spine
CST
STT
DCs always spared
CSTs spared until syrinx very large
STTs always affected since their fibres cross through the syrinx
Nerve roots at sequential levels invariably affected

Figure 3.78 Syringomyelia and syringobulbia. CST, corticospinal tract; DC, dorsal column; STT, spinothalamic tract.

Recognition

The slowly expanding central canal of syringomyelia results in those signs in Figure 3.78.

- The spinothalamic tracts are always affected because their fibres cross near the centre of the cord leading to *loss of hot/cold discrimination and pain sensation in a 'cape' distribution*. This is often the earliest sign.
- There is bilateral *wasting and weakness of the small muscles of the hands* due to bilateral compression of T1 ventral nerve roots. The syrinx generally originates in the cervical cord. Other anterior horn cells and nerve roots are affected as it elongates, resulting in *loss of upper limb reflexes and flaccid tone*.
- The dorsal columns are spared because they are too far from the site of disease. Because vibration, joint position and fine touch sense are preserved but pain and temperature sense are lost, the sensory loss is referred to as *dissociated sensory loss*.
- The corticospinal tracts may rarely be affected in late disease, resulting in spastic paraparesis or tetraparesis.

Interpretation

Confirm the diagnosis

Diabetes (foot and ankle joints) and tabes dorsalis (knee joints) can also cause Charcot's joints. The clue to syringomyelia should be the dissociated sensory loss.

What to do next – assess other systems

Other features that may be present are Horner's syndrome, Charcot's joints and other skeletal abnormalities:

- Horner's syndrome is common because the syrinx disrupts the sympathetic nerve fibres, especially at C8, T1
- In longstanding disease loss of pain sensation causes Charcot's joints
- Other skeletal abnormalities include kyphoscoliosis and cervical ribs. *La main succulemente* is the term given to the cold, swollen, dystrophic hands that may occur in syringomyelia as a result of autonomic vasomotor disturbance.

Consider severity/decompensation/complications

In syringobulbia the syrinx originates in the brainstem or extends upwards into it. There may be:

- Facial dissociated sensory loss (the decussating pain and temperature fibres from the descending trigeminal nucleus are affected)
- Wasting and weakness in the bulbar muscles giving rise to a bulbar palsy
- Nystagmus and cerebellar ataxia.

Consider function

Tell the examiners you would determine the level of disability and, as well as identifying and correcting any correctable cause, work closely with physiotherapy and occupational therapy colleagues to optimise function.

Discussion

What is the differential diagnosis of syringomyelia?

Syringomyelia is rare and has an equal sex incidence and an age of onset in early middle age. Intramedullary tumours of the spinal cord may cause a similar clinical picture to syringomyelia.

CASE 3.36 ABSENT ANKLE JERKS AND EXTENSOR PLANTARS

Instruction

Please examine this patient's legs (you may be asked specifically to examine reflexes and sensation) and discuss your findings.

Recognition

This implies no more than a combination of lower and upper motor neurone disease, described classically in:

- Subacute combined degeneration of the cord
- Taboparesis
- Friedreich's ataxia.

But most commonly these signs are visible when two common conditions occur together, e.g. cervical myelopathy causing extensor plantar responses and diabetes causing peripheral neuropathy with loss of ankle reflexes. Motor neurone disease and lesions at the conus medullaris may also cause a combination of upper and lower motor neuron signs.

Interpretation

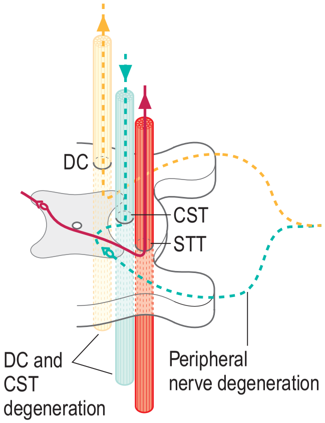
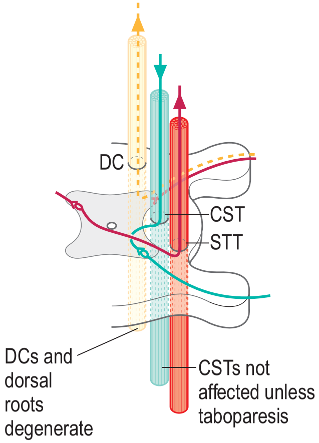
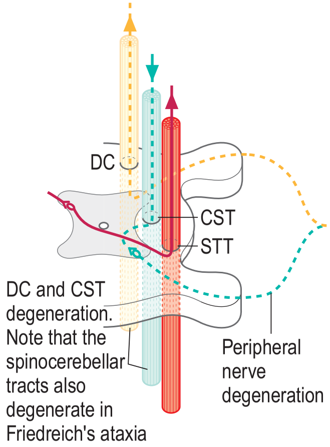
Confirm the diagnosis

A positive Romberg's sign (unsteadiness with the eyes closed or sensory ataxia) confirms dorsal column disease.

What to do next – consider causes

The three classic causes are differentiated by the clinical signs in Table 3.43. Though classic, they are not inevitable. It is perfectly possible, for example, to have Friedreich's ataxia with flexor plantars and without dorsal column involvement.

Table 3.43 Differentiating clinical signs of causes of absent ankle jerks and extensor plantars

	Subacute combined degeneration of cord (SACDC)	**Tabes**	**Friedreich's ataxia**
	 DC CST STT DC and CST degeneration Peripheral nerve degeneration	 DC CST STT DCs and dorsal roots degenerate CSTs not affected unless taboparesis	 DC CST STT DC and CST degeneration. Note that the spinocerebellar tracts also degenerate in Friedreich's ataxia Peripheral nerve degeneration
Dorsal columns (DCs)	Degenerate Loss of vibration and proprioception over feet (+/– legs and hands) +ve Romberg's sign	Degenerate Signs as for SACDC Without CST involvement = tabes dorsalis	Degenerate Signs as for SACDC
Corticospinal tracts (CSTs)	Weakness Extensor plantars Possible brisk knee reflexes (i.e. spastic paraparesis) Ankle reflexes absent because full-blown upper motor neuron picture prevented by peripheral nerve damage (loss of dorsal root ganglion cells)	If CSTs involved signs as for SACDC = taboparesis	Signs as for SACDC
Spinothalamic tracts (STTs)	Spared or involved as part of peripheral neuropathy	Spared	Spared
Other possible differentiating features	Optic atrophy with centrocaecal scotoma Dementia Autoimmune disease (if due to pernicious anaemia)	Ultimately neuropathic joint destruction – Charcot's joints, and trophic ulceration Argyll Robertson pupils Autonomic degeneration with neuropathic bladder and constipation Optic atrophy (rare)	Skeletal deformity – pes cavus, kyphoscoliosis Cerebellar signs, e.g. ataxia with wide-based gait, dysarthria Cardiomyopathy Diabetes

Consider severity / decompensation / complications

The spectrum of severity in each of the conditions is highly variable. Note in the final row of Table 3.43 the additional complications that may occur.

Consider function

Tell the examiners you would determine the level of disability and, as well as identifying and correcting any correctable cause, work closely with physiotherapy and occupational therapy colleagues to optimise function.

Discussion

What causes subacute combined degeneration of cord (SACDC)?

Vitamin B12 is a co-enzyme for transmethylation in DNA and myelin protein synthesis. Vitamin B12 deficiency may cause an array of insidious neurological problems including SACDC, pure peripheral neuropathy (often precedes SACDC) and dementia.

What are the stages of syphilis?

These are outlined in Box 3.48.

Syphilis is caused by the spirochaete *Treponema pallidum*, which can reach the central nervous system early in the course of infection, even in the primary stage. In meningovascular syphilis, leptomeningeal exudates, granulomata and arteritis produce progressive spastic paraparesis and radicular pain is common. In tabes dorsalis, a cellular reaction in the dorsal roots causes retrograde sensory loss up to 20 years after infection; characterised by lancinating pain that may be viscerally sited, then hypoalgesia.

Box 3.48 **Stages of syphilis**

- Primary chancre or ulcer, presenting within weeks.
- Secondary infection (fever, macular rash of hands and feet, condylomata lata, generalised lymphadenopathy and, less commonly, patchy alopecia, anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periostitis, glomerulonephritis), occurring within 2 years.
- Latent syphilis, diagnosed on serological testing with no symptoms or signs. It is early latent syphilis within the first 2 years, late latent syphilis beyond.

About one-third of untreated patients develop symptomatic late syphilis; this is categorised into neurosyphilis (tabes dorsalis, generalised paralysis), cardiovascular syphilis (aortitis) and gummatous syphilis but these may coexist. Tertiary syphilis is a term often used synonymously with symptomatic late syphilis, but generally excludes meningovascular syphilis; it is non-infectious.

Congenitally acquired syphilis is still problematic worldwide and appears to be increasing.

How is syphilis diagnosed?

Dark-ground microscopy (DGM) allows prompt diagnosis of syphilis. Polymerase chain reaction for *Treponema pallidum* in genital ulcers is available but should not replace DGM or serological tests (various). Two groups of serological tests are available, treponemal or specific (enzyme immunoassay to detect immunoglobulin G / M, *T. pallidum* haemagglutination assay, *T. pallidum* particle agglutination assay, fluorescent treponemal antibody absorbed test, *T. pallidum* recombinant antigen line immunoassay) and non-treponemal or non-specific (Venereal Diseases Research Laboratory carbon antigen test, rapid plasma reagin test), outlined in Table 3.44. Patients with symptoms or signs of possible neurosyphilis should have cerebrospinal fluid examination.

How is syphilis treated?

The treatment of choice is penicillin.

What do you know about Friedreich's ataxia?

This constitutes 50% of all inherited ataxias. It is an autosomal recessive spinocerebellar degeneration (referring not to spinocerebellar tracts in isolation, but to degeneration of multiple tracts within the spinal cord together with cerebellar degeneration) caused by an increased number of GAA trinucleotide repeat sequences at a gene encoding the protein frataxin on chromosome 9–9q13. Diagnostic criteria alongside gene testing include progressive ataxia starting under 25 years of age, absent lower limb reflexes and electrodiagnostic evidence of axonal neuropathy.

What are the spinocerebellar tracts?

These tracts convey unconscious proprioceptive information to the cerebellum. This is in contrast to the dorsal columns transmitting conscious sensation directly to the sensory cortex.

Table 3.44 Serological tests in syphilis

EIA	TPPA	RPR	FTA	Diagnosis
+	–	–	+	Early primary syphilis
+	+	–	+	Treated syphilis or untreated latent (early or late) syphilis
+	–	+	+	Primary syphilis
–	–	+	–	Biological false positive
+	–	–	–	Likely false positive

EIA, enzyme immunoassay; FTA, fluorescent treponemal antibody; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

CASE 3.37 MOTOR NEURONE DISEASE

Instruction

Please examine this patient's arms and legs and then discuss your findings.

Recognition

There is *asymmetrical muscle wasting and weakness* in the *limbs* (e.g. foot drop, weakness of the small muscles of the hand) (Fig. 3.79).

Interpretation

Confirm the diagnosis

Motor neurone disease (MND) is an adult-onset neurodegenerative disorder that leads to progressive weakness of limb, bulbar and respiratory muscles. MND should be in the differential diagnosis of a patient with weight loss, muscle wasting or weakness that is not otherwise easily explained. The hallmark is muscle weakness or wasting with preserved or brisk reflexes.

Classification of MND

In the UK the term MND collectively refers to three forms of the disease: amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS):

- ALS is by far the most common and involves loss of upper and lower motor neurons (UMNs and LMNs), producing a characteristic mixed picture.
- PMA is a disease predominantly of the LMNs although late in disease UMN features may develop.
- PLS is the rarest form of MND and predominantly involves UMNs (characterised by ascending relatively symmetrical spasticity including the face – corticobulbar dysarthria or pseudobulbar palsy) and is associated with the best prognosis. Some LMN features may eventually develop.

Diagnosis

In the absence of a definitive test, diagnosis of MND is clinical. Electrophysiology lends support whilst other investigations help exclude mimics. Central to diagnosing ALS are progressive mixed UMN and LMN symptoms and signs. A simplified version of the updated El Escorial revised diagnostic criteria for ALS is given in Box 3.49.

ALS according to the revised EL Escorial criteria

The criteria further specify degrees of diagnostic certainty dependent upon assessment of extent of disease. To this end four central nervous system regions are defined – brainstem, cervical, thoracic and lumbosacral – and the signs to be sought in each region are given in Table 3.45. Clinically definite ALS based on clinical evidence requires the presence of UMN as well as LMN signs in three regions, clinically probable ALS in at least two regions with some

Box 3.49 **Diagnostic criteria for amyotrophic lateral sclerosis**

- Evidence of lower motor neuron degeneration by clinical, electrophysiological or neuropathological examination
- Evidence of upper motor neuron degeneration by clinical examination
- Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination
- Absence of electrophysiological and pathological and neuroimaging evidence of other diseases

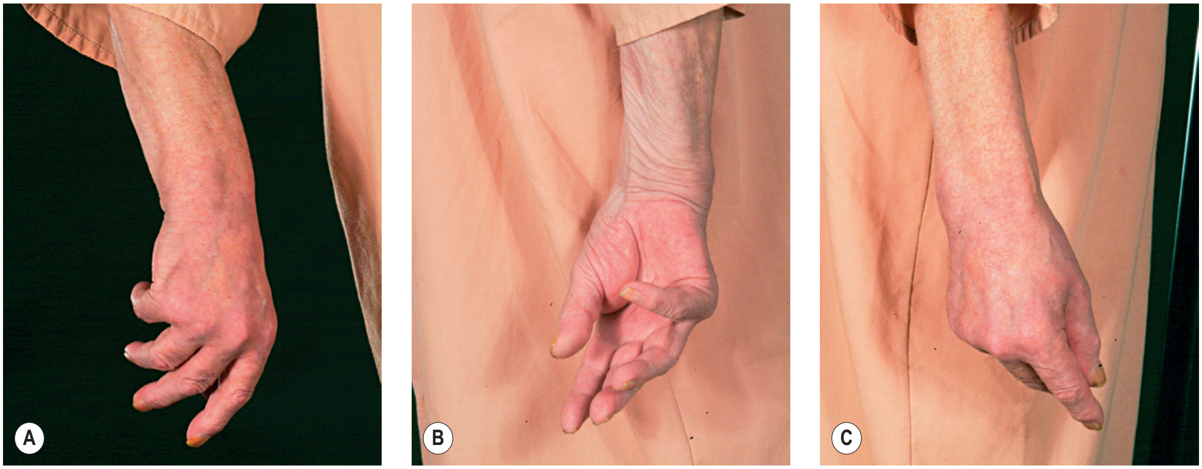


Figure 3.79 (A–C) Radial and ulnar nerve palsy and wasting in motor neurone disease.

Table 3.45 Upper motor neuron (UMN) and lower motor neuron (LMN) signs in the four central nervous system regions

Region	Brainstem*	Cervical†	Thoracic	Lumbosacral†
Body part	Face	Neck	Back	Back
	Jaw	Arm	Abdomen	Abdomen
	Palate	Hand		Leg
	Larynx	Diaphragm		Foot
	Tongue			
Lower motor neuron signs	Weakness	Weakness	Weakness	Weakness
	Atrophy	Atrophy	Atrophy	Atrophy
	Fasciculations	Fasciculations	Fasciculations	Fasciculations
Upper motor neuron signs	Clonic jaw	Brisk reflexes	Loss of abdominal reflexes	Brisk reflexes
	Gag reflex	Clonic reflexes	Spastic tone	Clonic reflexes
	Exaggerated snout reflex	Hoffman reflex		Extensor plantars
	Pseudobulbar palsy	Spasticity		Preserved reflex in weak and wasted lower limb
	Forced yawning	Preserved reflex in weak and wasted upper limb		
	Spastic tone			

*Progressive bulbar palsy is a form of amyotrophic lateral sclerosis with predominant bulbar involvement and causes drooling (sialorrhoea, because of impaired swallowing) and dysarthria and risk of nasal regurgitation of liquids.

†Presentation is often in an arm or leg, with a mixture of UMN and LMN signs. Brisk reflexes, fasciculation (commonly in the deltoid, first dorsal interosseous and thigh muscles), corticobulbar signs with a brisk jaw jerk, and extensor plantar reflexes are common. LMN disease predominantly affecting upper (flail arm) and lower (flail leg) limbs is also recognised.

UMN signs above the LMN signs. By the time patients meet criteria they are, by definition, at an advanced stage.

Red flags to diagnosis

- Sensory signs are not present in any form of MND.
- Motor neurons serving the extraocular muscles and pelvic floor are spared in all forms of MND so that ocular palsies and sphincter disturbance are never present.
- Weakness out of proportion to wasting or that is atypical in pattern should prompt consideration of alternative diagnoses. Uncommonly MND may be associated with extra-motor features.

What to do next – assess other systems

Tell the examiners that you would assess respiratory function (spirometry) and swallowing (speech and language therapist).

Consider severity / decompensation / complications

Prognosis in MND is wide. Muscle wasting leads to progressive weakness, with respiratory function, swallowing and nutrition importantly affected. Death typically occurs 3–5 years from diagnosis, most often from respiratory failure.

Box 3.50 **Predictors of long-term survival in motor neurone disease**

- Pure lower or upper motor neurone disease
- Absence of bulbar involvement
- Absence of respiratory involvement
- Confined to specific regions, e.g. arm or leg for long period
- Slow progression in first year

Fifty per cent of patients with ALS die from respiratory failure, almost always peacefully, at a mean of 40 months from symptom onset, 20% are alive at 5 years and 10% at 10 years. Ten per cent of ALS is associated with a frontotemporal dementia and the rare Guamanian variant has additional extrapyramidal features.

A pure LMN form of MND confined to arms or legs for many years has a better prognosis, whilst more generalised LMN forms can be rapidly progressive.

PLS is often associated with long-term survival of beyond 15–20 years.

Predictors of long-term survival are shown in Box 3.50.

Consider function

This would be individually determined.

Discussion

How common is MND?

MND has an incidence of 1–2/100 000 and a prevalence of approximately 6/100 000. Onset is typically in late middle age. Increasing age, male sex (1.6 : 1) and the inheritance of a genetic susceptibility are the only proven risk factors. Approximately 90% is sporadic, the remainder inherited.

What causes MND?

This is not known. About 10% of MND is familial and most familial MND is autosomal dominant. Mutations to a ubiquitous antioxidant enzyme, Cu/Zn superoxide dismutase (SOD1), are responsible for approximately 20% of inherited MND but the mechanism of how the mutations promote motor neuronal death is unclear. Overexpression rather than loss of enzyme function in microglia (the main immune cells of the nervous system) may cause disease. Other responsible mutations include TAR DNA-binding protein (TARDBP) and fused in sarcoma or FUS, both of whose gene products are likely to have roles in RNA processing. TARDBP 43 is the main component of the pathological hallmark protein inclusions found in surviving motor neurons in sporadic MND (also in frontotemporal dementia and PMA). Astrocytes, cells which support neuronal structure and function, are responsible for reuptake of excitotoxic neurotransmitters such as glutamate, receptors for which may be aberrant in MND (the basis for riluzole therapy).

Which investigations may be considered in diagnosing MND?

All suspected MND patients should undergo electrophysiological testing which allows identification of LMN features of MND in both clinically affected and as yet clinically silent regions. Typical electromyographic features include evidence of active denervation (positive sharp waves, fibrillation potentials, fasciculation potentials) and chronic denervation evidenced by large motor unit potentials. In pure LMN syndromes evidence of alternative diagnoses, such as conduction block and demyelination, is sought. Conduction block can be particularly difficult to demonstrate. Interval studies may be needed. Magnetic resonance imaging (MRI) of the spinal cord should be done in all limb-onset ALS patients without bulbar involvement as mixed cord and root compression is responsible for some 30% of ALS misdiagnoses. When symptoms and signs are isolated to the bulbar region MRI can identify infiltrative lesions of the tongue and pharynx. Some differential diagnoses of MND are listed in Table 3.46.

Summarise the management of MND

MND is best managed within specialist centres offering multidisciplinary care.

Table 3.46 Differential diagnoses of motor neurone disease (MND)

Form of MND	Mimic	Clues in differentiation
Amyotrophic lateral sclerosis	Multilevel spinal cord and root compression by discs, osteophytes or tumour	Sensory symptoms and pain common UMN often caudal to LMN signs MRI spine
	Combined peripheral neuropathy and cervical myelopathy	MRI spine and electrophysiology
	Paraneoplastic syndromes (especially lymphoma)	Computed tomography chest/abdomen Tumour markers Cerebrospinal fluid studies
	Thyrotoxicosis	Non-motor symptoms and signs Thyroid function tests
	Inclusion body myositis	Rare Pattern of weakness affects long finger flexors and quadriceps early Muscle biopsy
	Radiation myelopathy	History MRI spine
	Structural lesions of the bulbar region	Failure to progress beyond region MRI

Table 3.46 Differential diagnoses of motor neurone disease (MND)—cont'd

Form of MND	Mimic	Clues in differentiation
Progressive muscular atrophy	Chronic idiopathic demyelinating polyneuropathy	Electrophysiology identifies demyelination
	Multifocal motor neuropathy	Weakness out of proportion to wasting NCS can identify conduction block Anti-GM1 antibodies may be raised
	Acute motor axonal neuropathy (a Guillain–Barré variant)	Acute onset and progression NCS
	Compressive focal neuropathies	Sensory involvement common Failure to extend beyond territory of one nerve Electrophysiology helpful
	Lead poisoning	Extramotor clinical features, e.g. constipation, nail and mouth signs Lead levels
	Porphyria	Extra-motor clinical features Episodic Family history Stool testing
	Lyme disease	Non-neurological symptoms and signs, e.g. rash Borrelia testing
	Hereditary motor neuropathies	Pure LMN syndrome Slower progression Family history
	Kennedy's disease	Possible gynaecomastia, sensory symptoms or peri-oral fasciculations Slower progression Genetic testing
	Spinal muscular atrophy	Can be adult-onset Pure LMN syndrome Slower progression Genetic testing
	Benign cramp fasciculation syndrome	Predominantly middle-aged men Largely calf involvement Failure to progress No active denervation on EMG
	Post-polio syndrome	Pure LMN syndrome Past history or EMG confirms previous polio
Primary lateral sclerosis	Multiple sclerosis	Non-motor symptoms and signs, e.g. eye, bladder, cerebellar, sensory MRI brain and spine
	Spinal cord compression	Sensory involvement and pain common MRI spine
	Hereditary spastic paraplegia	Prominent bladder symptoms Family history Genetic testing

EMG, electromyography; LMN, lower motor neuron; MRI, magnetic resonance imaging; NCS, nerve conduction studies; UMN, upper motor neuron.

Disease-modifying therapy

Riluzole is the only disease-modifying therapy in MND, evidenced in ALS. It reduces presynaptic glutamate release. Other neuroprotective effects are likely to contribute. On average riluzole extends life by 3–4 months although subsets of patients may benefit more.

Other therapy

This is outlined in Table 3.47. Nutritional and respiratory management of MND patients have an impact upon prognosis and require careful multidisciplinary specialist input.

Table 3.47 Symptomatic management

Problem	Management
Nutrition	dietitian Gastrostomy tube placed via endoscopy or using ultrasound guidance (radiologically inserted gastrostomy)
Breathing	Baseline lung function tests at diagnosis and FVC at each visit Aspiration pneumonia identified and treated early with chest physiotherapy and antibiotics Cough assist machine and carbocysteine to help with sputum Patients generally symptomatic from respiratory muscle weakness once FVC ≤ 50% of expected – non-invasive positive pressure ventilation confers survival benefit and improves quality of life in patients with normal or moderately impaired bulbar function Sublingual lorazepam for acute dyspnoea or laryngospasm Morphine for end-stage respiratory distress
Difficulty swallowing with drooling	Suction, amitriptyline, hyoscine patches, atropine, botulinum toxin injection into salivary glands
Proximal arm weakness	Mobile arm supports, modified cutlery
Spasticity	Baclofen, diazepam, tizanidine
Cramps	Quinine
Fatigue	Pyridostigmine
Constipation	Aperients
Depression	Antidepressants
Pain	Optimisation of seating and positioning, physiotherapy, analgesia

FVC, forced vital capacity.

CASE 3.38 CERVICAL MYELORADICULOPATHY

Instruction

Please examine this patient's arms and legs and then discuss your findings.

Recognition

There is *weakness* and *increased tone in the lower limbs* with *enhanced reflexes* and *extensor plantar responses*. There may be sensory impairment (compression of dorsal columns). There may be inversion of the biceps and supinator reflexes. In middle-aged to older patients the most likely diagnosis is cervical spondylosis.

Box 3.51 **Inverted reflexes**

This is a phenomenon caused by combined spinal cord and root disease. It simply means absent reflexes at the segmental level of the lesion and enhanced reflexes below. With an inverted biceps reflex (C5/6 segment lesion), when the biceps tendon is tapped there is no biceps reflex but the triceps (C7) may be stimulated by the manoeuvre. In an inverted supinator reflex (C5/6) there is no supinator response but finger flexion (C8) may be seen to have been stimulated.

Interpretation

Confirm the diagnosis

The most common level of cervical spondylosis is C5, 6. Always check for inversion of the biceps and supinator reflexes (Box 3.51). Upper motor neuron signs are present below the level of the lesion, giving rise to brisk triceps (C7) and finger (C8) reflexes.

What to do next – consider causes

If there is spastic paraparesis or tetraparesis, the numerous differential diagnoses are given in Case 3.34.

Consider severity/decompensation/complications

Tell the examiners that you would ask about sphincter disturbance (bladder or bowel symptoms, urinary catheter) and initially exclude acute cord compression, a neurosurgical emergency.

Consider function

Tell the examiners you would determine the level of disability and, as well as identifying and correcting any correctable cause, work closely with physiotherapy and occupational therapy colleagues to optimise function.

Discussion

What is cervical spondylosis? (Fig. 3.80)

Cervical spondylosis is the most common cause of cervical myeloradiculopathy, and the signs are frequently subtle. It is often painless and may be suspected with brisk lower limb reflexes but minimal or no other neurological signs. Sometimes it gives rise to Lhermitte's phenomenon, with a burning sensation on neck flexion. Commonly C5/6 is affected with signs of radiculopathy at that level and signs of myelopathy below. The cervical and lumbar spine is subjected to most movement with greater propensity to degeneration over a lifetime than the thoracic spine.

What do you know about disc prolapse?

Cervical disc lesions may provoke cervical myeloradiculopathy. Cervical disc prolapse is more common in young to middle-aged adults, and especially affects vertebral levels C5/C6 and C6/C7, with marked radicular pain. Lumbosacral disc prolapse is much more common and causes

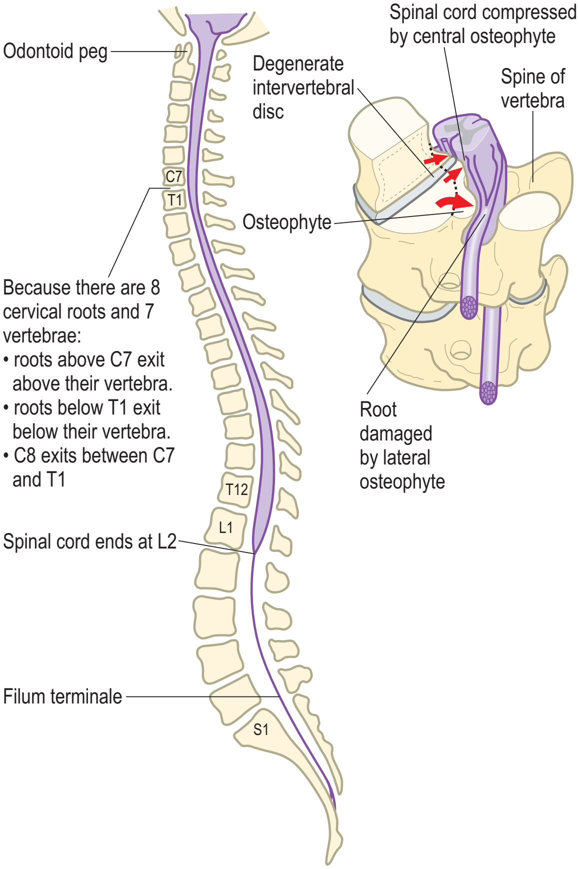

Odontoid peg
Degenerate intervertebral disc
Spinal cord compressed by central osteophyte
Spine of vertebra
C7
T1
Osteophyte
Because there are 8 cervical roots and 7 vertebrae:
• roots above C7 exit above their vertebra.
• roots below T1 exit below their vertebra.
• C8 exits between C7 and T1
Root damaged by lateral osteophyte
T12
L1
Spinal cord ends at L2
Filum terminale
S1

Figure 3.80 Spinal cord, roots and compression.

radiculopathy but not myelopathy because the spinal cord has terminated at the lower level of the L1 vertebra.

CASE 3.39 CAUDA EQUINA SYNDROME

Instruction

Please examine this patient's legs and then discuss your findings.

Recognition

There is *flaccid weakness* in the lower limbs with *loss of the knee and ankle reflexes* and *normal plantar responses*. There is *dermatomal sensory loss below L1*. These findings suggest a complete cauda equina lesion.

Interpretation

Confirm the diagnosis

A lesion in the spinal canal below the conus medullaris can cause a cauda equina syndrome. Because the spinal cord ends as the conus medullaris at the lower end of the L1 vertebra, the lumbar and sacral roots pursue a long course (unlike cervical roots) within the lumbar vertebral canal and can be injured anywhere within it to their intervertebral foramina exit sites. Cauda equina syndrome results from dysfunction of multiple sacral and lumbar nerve roots in the lumbar vertebral canal (rather than single root lesions), and by definition the term cauda equina syndrome is used only when dysfunction includes impairment of bladder, bowel or sexual function, and perianal or 'saddle' numbness (Box 3.52).

Flaccid weakness and areflexia in the lower limbs can be the result of Guillain–Barré syndrome. Tell the examiners that you would take a history for ascending symptoms over a few days. Overt sensory loss is not a feature of Guillain–Barré syndrome.

Box 3.52 **Clinical diagnosis of cauda equina syndrome**

- Dysfunction of bladder, bowel or sexual function
- Sensory changes in saddle or perianal area

Other possible symptoms

- Back pain (with or without sciatic-type pain)
- Sensory changes or numbness in the lower limbs
- Lower limb weakness
- Reduction or loss of reflexes in the lower limbs
- Unilateral or bilateral symptoms

What to do next – consider causes / assess other symptoms

Cauda equina syndrome may be classified by location, presentation or clinically.

Location

- Midline, with bilateral symptoms
- Lateral, often with unilateral root symptoms

Presentation

- Acutely as the first symptom of lumbar disc herniation
- As the endpoint of a long history of chronic back pain with or without sciatica
- Insidiously with slow progression to numbness and urinary symptoms (primary or metastatic spinal neoplasms are often accompanied by marked pain, often chronic)

It is postulated that there is relative hypovascularity at the proximal portion of the cauda equina such that reduced blood supply from nerve root pressure here may be of greater importance than elsewhere, with rapid changes allowing less adaptation than those of a slower onset.

Clinically

- Cauda equina syndrome with urinary retention
- Incomplete cauda equina syndrome, with reduced urinary sensation, loss of desire to void,

or a poor stream, but no established retention or overflow

Most clinicians now classify cauda equina syndrome clinically. Often the slower the presentation, the better tolerated the symptoms are and the less likely the patient to be alarmed. Those with pre-existing bladder problems resulting from other disease may also present late. Cauda equina lesions and their causes and clinical features are outlined in Table 3.48. Lumbar intervertebral disc prolapse causing isolated radiculopathies is very common. For example, the highly prevalent L4/5 and L5/S1 disc prolapses compress the L5 or S1 roots at their exit foraminae (although these roots originated from their cord segment at a much higher level). The term cauda equina syndrome suggests more widespread damage arising within the canal involving multiple nerve roots and with associated sphincter disturbance and perianal numbness. Only a small number of herniated discs are likely to cause cauda equina syndrome, although because disc herniation is so common overall it is probably the commonest cause. Pain in the distribution of L4, L5 or S1 without sphincter disturbance or perianal numbness may reasonably be attributed to lumbosacral disc disease, but widespread root disturbance, root pain in unusual dermatomes or evidence of higher lumbar disc disease or lower sacral root damage is unusual, and should ring alarm bells to possible cauda equina syndrome.

Consider severity / decompensation / complications

Tell the examiners that you would ask about sphincter disturbance (bladder or bowel symptoms, urinary catheter) and initially exclude acute cord compression, a neurosurgical emergency. Tell the examiners that a full neurological examination (not to be performed in PACES) of the legs, and assessment of perianal sensation and of anal tone should be performed (Table 3.49).

Consider function

Tell the examiners you would determine the level of disability and, as well as identifying and correcting any correctable cause, work closely with physiotherapy and occupational therapy colleagues to optimise function.

Discussion

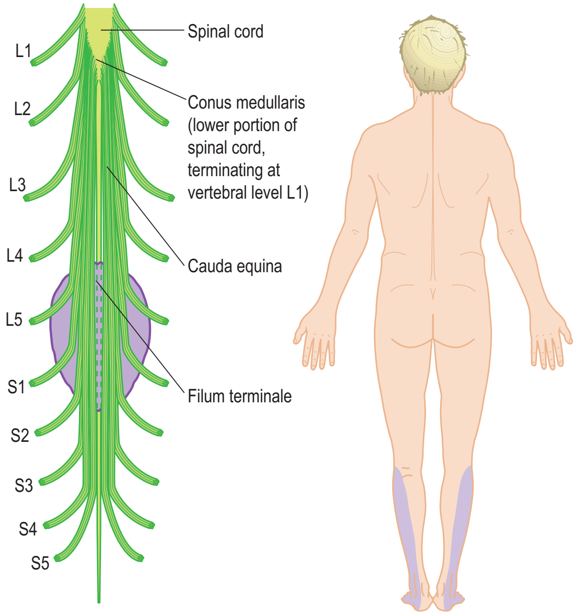
What is the conus medullaris?

This is the terminal portion of the spinal cord, at vertebral level L1, and from it emerge the lower sacral roots.

What is the cauda equina?

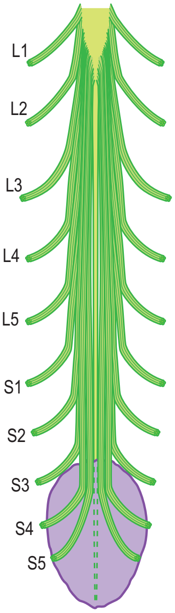
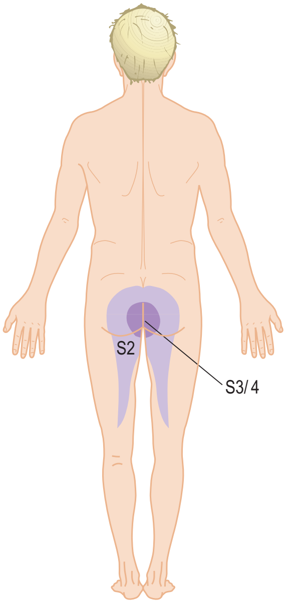
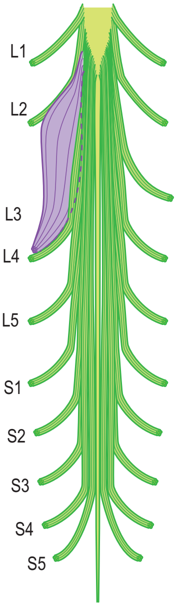
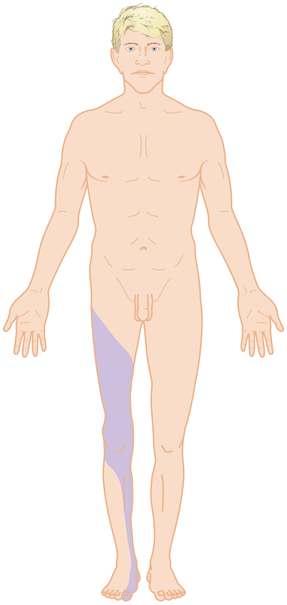
The spinal cord is shorter than the vertebral column, its roots sloping inferiorly from their levels of origin to their

Table 3.48 Cauda equina lesions

	Type	Causes	Features
	Midline extrinsic lesion	Compression from large central lumbar disc herniation at L4/5 and L5/S1 +/− other levels Spinal injury with fractures or subluxation Abscess Tuberculosis of spine (Pott's paralysis) Bone metastases Sacral tumour Spinal manipulation Spinal anaesthesia Postoperative haematoma Predisposition – congenitally narrow spinal canal or acquired spinal stenosis from degenerative discs and segmental posterior joints with consequent thickening of ligamentum flavum and narrowing of canal	Any pattern of root disturbance Sphincter disturbance Saddle numbness

L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Spinal cord
Conus medullaris (lower portion of spinal cord, terminating at vertebral level L1)
Cauda equina
Filum terminale

Table 3.48 Cauda equina lesions—cont'd

	Type	Causes	Features
 	Midline intrinsic lesion	Dermoid tumour Ependymoma Lipoma	Roots damaged from 'inside out', i.e. S5 → S4 → S3 and so on Rectal pain Genital pain Sphincter disturbance Saddle anaesthesia
 	Lateral lesion	Neurofibroma	Dermatomal pain (e.g. anterior thigh pain) Wasting (e.g. quadriceps) Weakness (e.g. ankle inversion with L4 lesion) Absent reflex (e.g. ankle reflex) Enhanced ankle reflexes and extensor plantars if terminal cord compressed Sphincter disturbance

designated intervertebral foraminae, especially further down the cord. Below the inferior end of the cord, the dural–arachnoid sac contains a leash of roots (T12–S5) and the filum terminale – a complex called the cauda equina ('horsetail').

Can lumbar disc disease cause upper motor neuron signs?

Because the spinal cord ends at the L1 vertebral level, lumbar disc disease should never cause upper motor neuron signs.

Table 3.49 Motor, sensory and reflex components of lumbar and sacral roots

Nerve root	Motor	Sensory	Reflexes
L2	Hip flexors Thigh adductors	Upper thigh	
L3	Quadriceps Knee extensors	Lower and anterolateral thigh	
L4	Knee extensors	Anteromedial calf	Patella, knee
L5	Knee flexors Foot and toe dorsiflexors	Lateral calf Dorsum of foot	
S1, S2	Foot and toe plantar flexors	Lateral side of foot Sole of foot	Ankle
S2, S3, S4, S5	Sphincters	Perianal and saddle	Bulbocavernosus (genital stimulation causes reflex contraction of anal sphincter, mediated through sacral roots)

How should suspected cauda equina syndrome be investigated?

Magnetic resonance imaging (MRI) is the imaging modality of choice. It does not define bone as clearly as computed tomography but is better at showing soft tissues such as intervertebral disc, ligamentum flavum, dural sac, and nerve roots.

How is cauda equina syndrome treated?

Urgent surgical referral for suspected cauda equina syndrome is vital. When a patient has clinical features consistent with cauda equina syndrome and the MRI shows a potentially reversible cause of pressure on the cauda equina then surgical decompression is recommended. Most cases of cauda equina syndrome are caused by herniation of a lumbar disc, for which decompression at the level of the herniation, usually involving discectomy, is necessary. The urgency of surgery remains controversial. If there is pressure on the cauda equina causing loss of sphincter control, it would seem intuitive to remove the pressure as soon as possible. Some suggest that only incomplete cauda equina syndrome requires emergency surgery to try to thwart deterioration in bladder function but that cauda equina syndrome with retention has a poor clinical outcome anyway. Some suggest that incontinence at presentation is a poor prognostic feature.

CASE 3.40 CARPAL TUNNEL SYNDROME (MEDIAN NERVE LESION)

Instruction

Please examine this patient's hands and discuss your findings.

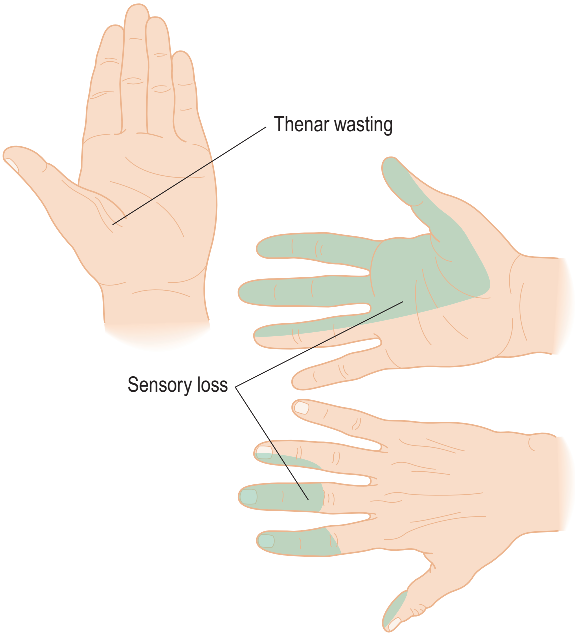


Figure 3.81 Thenar wasting and sensory loss in a median nerve lesion.

Recognition

There is *thenar wasting*. There is *weakness of opposition, abduction and flexion of the thumb* and weakness of the index and middle finger lumbricals. *Sensation is impaired over the palmar aspect of the lateral side of the hand, thumb, index finger, middle finger and lateral (radial) border of the ring finger* (Fig. 3.81).

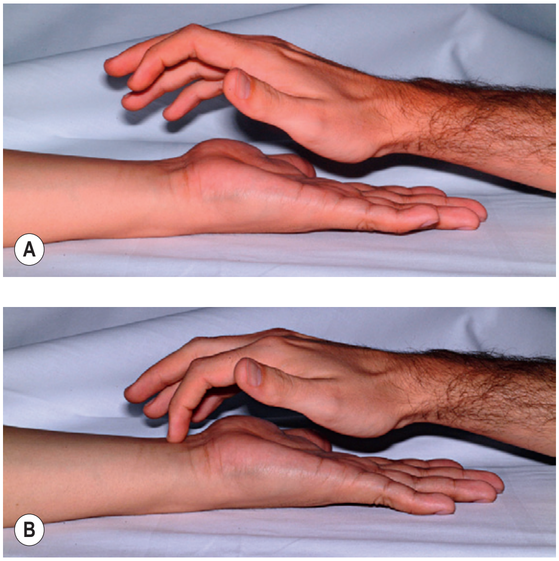


Figure 3.82 (A, B) Eliciting Tinel's sign.

Box 3.53 **Causes of carpal tunnel syndrome**

- Often idiopathic entrapment
- Diabetes
- Connective tissue disease, e.g. rheumatoid arthritis
- Hypothyroidism
- Acromegaly
- Pregnancy
- Osteoarthritis
- Amyloid
- A family history of small carpal tunnels

Interpretation

Confirm the diagnosis

Tell the examiners you would ask about symptoms, particularly nocturnal pain or tingling, which often radiates up the forearm. Percussing over the median nerve at the wrist may reproduce the tingling – Tinel's sign (Fig. 3.82). Flexing the wrist for 1 minute may do the same (Phalen's sign). Neither of these eponymous signs has been discriminating in clinical studies.

Clinical tests predictive of neurophysiological evidence of a median nerve lesion include:

- Hyperalgesia in the median nerve territory
- The classic Katz hand diagram (patient draws the area of sensory loss)
- Weakness of abductor pollicis brevis.

What to do next – consider causes

Causes of carpal tunnel syndrome are listed in Box 3.53.

Table 3.50 The median nerve

Roots supplying the median nerve	Muscles supplied by these roots	Common sites of a median nerve lesion
C6	Forearm pronators	Carpal tunnel (carpal tunnel syndrome) Wrist (lacerations, trauma) Forearm (fractures) Elbow (fractures/dislocations)
C7	Lateral wrist flexors – flexor carpi radialis	
C8	Long finger flexors (via anterior interosseous branch of median nerve) – FDPs to index and middle fingers, FDSs to index and middle fingers, flexor pollicis longus	
T1	'LOAF' intrinsic muscles of the hand (p. 508)	

FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; LOAF, lateral two lumbricals, opponens pollicis, abductor pollicis brevis, flexor pollicis brevis.

Consider severity/decompensation/complications

Worsening weakness may be more of an imperative than sensory symptoms.

Consider function

Tell the examiners how you think it might affect the patient's life, especially the nocturnal discomfort.

Discussion

What is the nerve root supply to the median nerve?

See Table 3.50.

Which muscles are supplied by the median nerve?

See Table 3.50.

Which common sites are affected in median nerve palsy?

See Table 3.50.

Are the signs of a median nerve lesion different if the lesion is at or above the elbow?

There may be lateral forearm wasting and the index (+/− middle) finger is held in extension (Benediction attitude).

What is the investigation of choice?

A nerve conduction study is imperative before surgical decompression is contemplated.

How would you recognise an anterior interosseous nerve lesion?

An isolated lesion of the anterior interosseous nerve, albeit rare, causes isolated weakness of pincer grasp.

What is the treatment for carpal tunnel syndrome?

Steroids, splinting and yoga may have modest benefits. Surgical decompression is the treatment of choice but benefit in severe lesions is uncertain and where other causes will settle or are treatable as in pregnancy or hypothyroidism, management is usually conservative.

CASE 3.41 ULNAR NERVE LESION

Instruction

Please examine this patient's hands and discuss your findings.

Recognition

There is *generalised wasting* of the hand muscles (Fig. 3.83), *sparing only* the *thenar eminence*. Look especially for *dorsal guttering*; the first dorsal interosseus is invariably the first muscle noticeably affected, causing hollowing of the first web space.

In a low ulnar nerve lesion the hand is claw shaped – the metacarpophalangeal joints of the ring and little fingers are hyperextended and the interphalangeal (IP) joints remain flexed. There is weakness in abduction and adduction of the fingers and thumb.

Sensation is impaired over the medial side of the hand, little finger and medial (ulnar) border of the ring finger (Fig. 3.84). Ulnar nerve palsy is illustrated in Figure 3.85.

Interpretation

Confirm the diagnosis

Consider other causes of wasting of the intrinsic muscles of the hand (Case 3.43).

What to do next – consider causes

Be sure that you can differentiate between a low and a high ulnar nerve lesion (Box 3.54; Fig. 3.86).

Consider severity / decompensation / complications

Worsening weakness may be more of an imperative than sensory symptoms.

Consider function

Tell the examiners how you think it might affect the patient's life – grip and so forth. Check for Froment's sign – ask the patient to grip a piece of paper or a book between the index finger and thumb (Fig. 3.87). Because thumb adduction is weak, the IP joint must flex to perform this task, possible because the flexor pollicis longus is supplied by the median nerve.

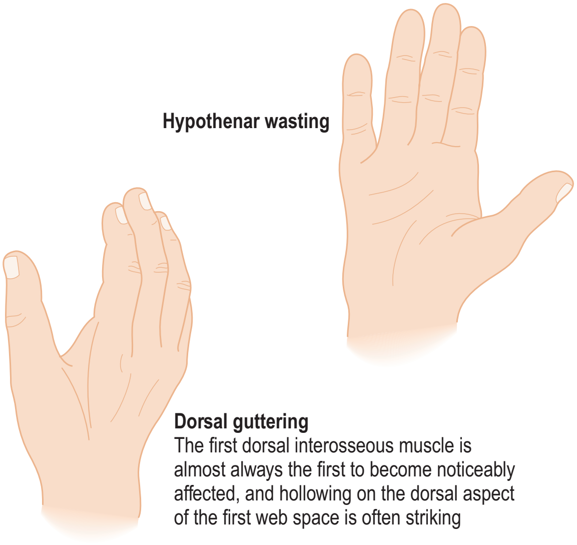

Hypothenar wasting
Dorsal guttering
The first dorsal interosseous muscle is almost always the first to become noticeably affected, and hollowing on the dorsal aspect of the first web space is often striking

Figure 3.83 Wasting in an ulnar nerve lesion.

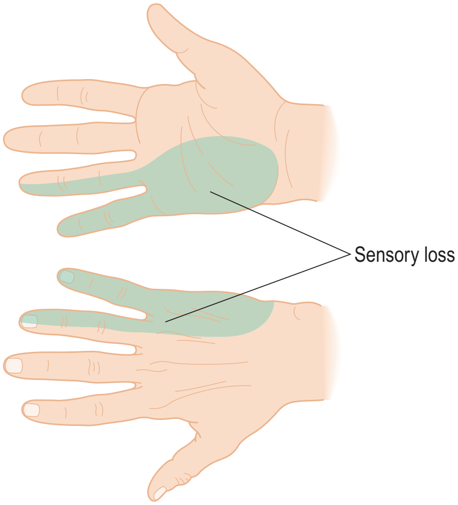


Figure 3.84 Sensory loss in an ulnar nerve lesion.

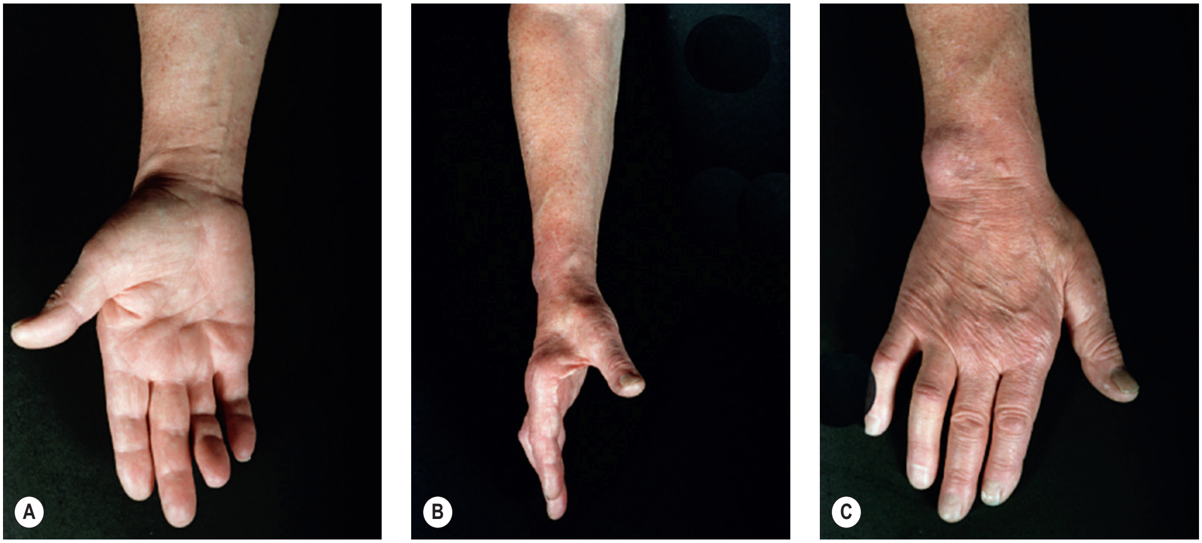


Figure 3.85 (A–C) Ulnar nerve palsy.

Box 3.54 **Differentiating low and high ulnar nerve lesions**

Low lesion

The hand is clawed. The lumbricals of the ring and little fingers are paralysed, causing hyperextension of the metacarpophalangeal joints, but the flexor digitorum profundus (FDP) muscless are intact and flex the distal interphalangeal (DIP) joints. The paralysed interossei also make a contribution to proximal interphalangeal flexion. Low lesions occur at the wrist.

High lesion (above the wrist)

The FDP muscles are also paralysed. The DIP joints are hence not flexed and so clawing is less obvious. This has been termed the ulnar paradox. High lesions occur commonly at the elbow and include osteoarthritis and fractures / dislocations. The ulnar nerve is particularly vulnerable in the cubital tunnel or ulnar groove. Some people are particularly prone to pressure palsy of the ulnar nerves, provoked by prolonged leaning on desks. As with all mononeuropathies, consider diabetes, connective tissue disorders and vasculitides.

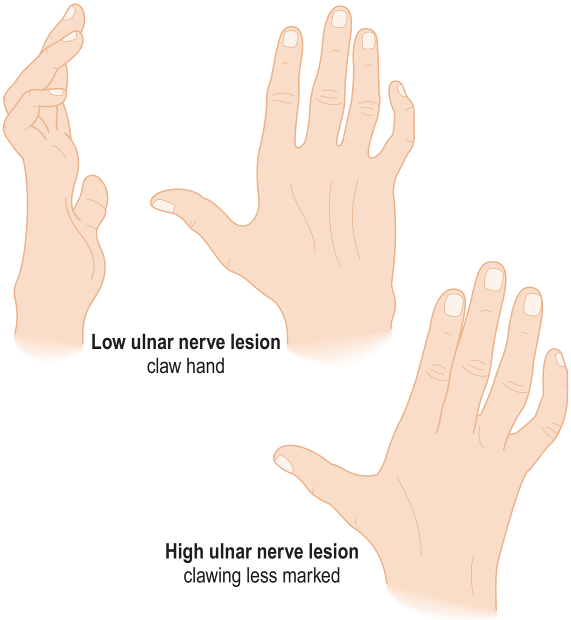


Figure 3.86 Claw hand.

Discussion

What is the nerve root supply to the ulnar nerve?

See Table 3.51.

Which muscles are supplied by the ulnar nerve?

See Table 3.51.

Which common sites are affected in ulnar nerve palsy?

See Table 3.51.

What is the differential diagnosis of a 'claw hand'?

Two conditions should always be considered:

- Volkmann's ischaemic contracture, usually a consequence of brachial artery damage by a supracondylar fracture
- Diabetic cheiropathy, a complication of longstanding type 1 diabetes mellitus, in which there is skin tightening, joint restriction and sclerosis of tendon sheaths.

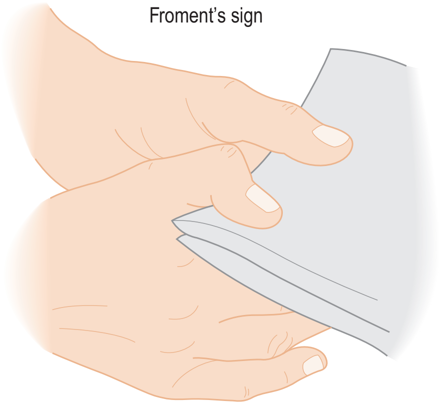


Figure 3.87 Normal and paralysed adductor pollicis giving rise to Froment's sign.

Table 3.51 The ulnar nerve

Roots supplying the ulnar nerve	Muscles supplied by these roots	Common sites of an ulnar nerve lesion
C8	Medial wrist flexors – flexor carpi ulnaris Long finger flexors – FDP and FDS to ring and little fingers	Ulnar tunnel, where the nerve passes between the pisiform and hamate bones (trauma, ganglion) Wrist (Guyon's canal – ganglion, laceration, trauma – increasingly seen in mountain bikers) Medial epicondyle (friction, pressure, stretching, osteoarthritis, trauma) Brachial plexus
T1	Intrinsic muscles of the hand other than the 'LOAF' muscles	

FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; LOAF, lateral two lumbricals, opponens pollicis, abductor pollicis brevis, flexor pollicis brevis.

Is leprosy still common?

Worldwide, leprosy remains a common cause of peripheral nerve thickening and damage, notably the greater auricular nerve and the ulnar nerve (Fig. 3.88).

What is the treatment for an ulnar nerve lesion at the elbow?

Most patients would be offered decompression, with or without transposition, with significant signs and not improving having avoided repeated minor trauma.

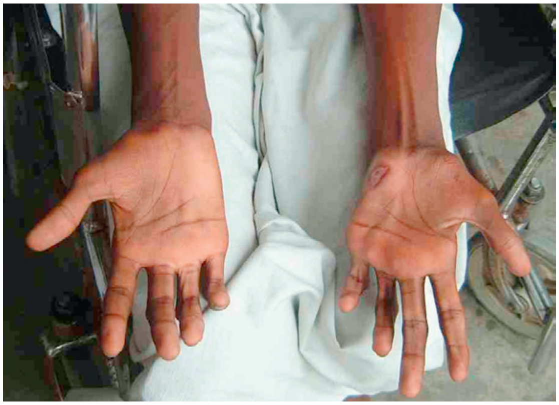


Figure 3.88 Bilateral ulnar nerve palsy in leprosy.

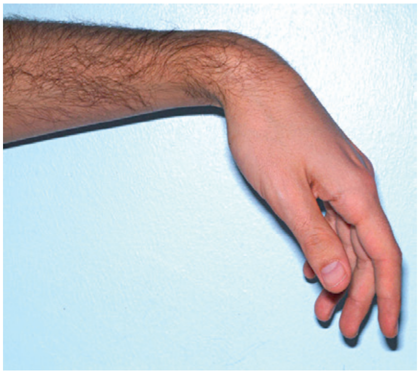


Figure 3.89 Wrist drop.

CASE 3.42 RADIAL NERVE LESION

Instruction

Please examine this patient's hands and discuss your findings.

Recognition

There is a *wrist drop* and *weakness of finger extension* (Fig. 3.89). There is *sensory impairment over the first dorsal interosseous* ('anatomical snuffbox', considerable sensory overlap with the other nerves meaning the area is small). Straightening fingers at the interphalangeal joints is made possible if the wrist is passively straightened because the intrinsic muscles of the hand supplied by the ulnar nerve (interossei and lumbricals) permit some extension. No extension is possible at the metacarpophalangeal joints.

Grip is impaired, not because any flexors are weak but because a degree of wrist extension facilitates good grip. Likewise, abduction and adduction of the fingers are

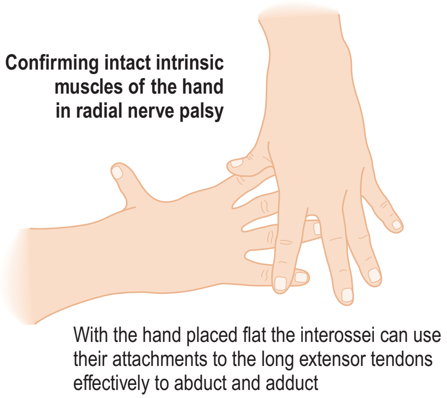

Confirming intact intrinsic muscles of the hand in radial nerve palsy
With the hand placed flat the interossei can use their attachments to the long extensor tendons effectively to abduct and adduct

Figure 3.90 Radial nerve lesion.

unaffected but may appear to be with a flexed wrist. Testing movements with the palm placed on a flat surface demonstrates that they are nicely intact (Fig. 3.90).

Interpretation

Confirm the diagnosis

Check elbow extension and the triceps reflex. An intact triceps reflex indicates a lesion below the spiral groove. Triceps wasting and an absent reflex imply a high (axillary) radial nerve lesion or a C7 radiculopathy. A C7 root lesion causes weakness of shoulder adduction, elbow extension, wrist flexion and wrist extension because it makes a significant contribution to both the median and radial nerves. A radial nerve lesion cannot affect shoulder adduction or wrist flexion.

What to do next – consider causes

This is the most common acute mononeuropathy, presenting after deep sleep or coma.

Consider severity / decompensation / complications

Worsening weakness may be more of an imperative than sensory symptoms.

Consider function

Tell the examiners how you think it might affect the patient's life.

Discussion

What is the nerve root supply to the radial nerve?

See Table 3.52.

Table 3.52 The radial nerve

Roots supplying the radial nerve	Muscles supplied by these roots	Common sites of a radial nerve palsy
C6	Supinator Brachioradialis	At or below the elbow (fracture, dislocation, ganglion) Shaft of humerus (fracture) Axilla (crutches, overnight 'stupor' paralysis caused by sleeping with arm slumped over chair)
C7	Elbow extensors – triceps Wrist extensors	
C8	Long finger extensors – extensor digitorum, extensor pollicis longus, extensor pollicis brevis	

Which muscles are supplied by the radial nerve?

See Table 3.52.

Which common sites are affected in radial nerve palsy?

See Table 3.52.

How would you recognise an axillary nerve lesion?

This is usually due to a traumatic lesion at the humeral head, and causes weakness of the deltoid and sensory loss over the lateral shoulder.

How would you recognise an isolated lesion of the posterior interosseous branch of the radial nerve?

This is rare, usually due to compression as the nerve enters the supinator muscle. It causes weakness of finger extension without a wrist drop or sensory loss. The differential diagnosis is a radiculopathy of C7.

CASE 3.43 WASTING OF THE SMALL (INTRINSIC) MUSCLES OF THE HAND

Instruction

Please examine this patient's hands and discuss your findings.

Recognition

There is *wasting and weakness of all the small or intrinsic muscles* (Fig. 3.91) of the hand.

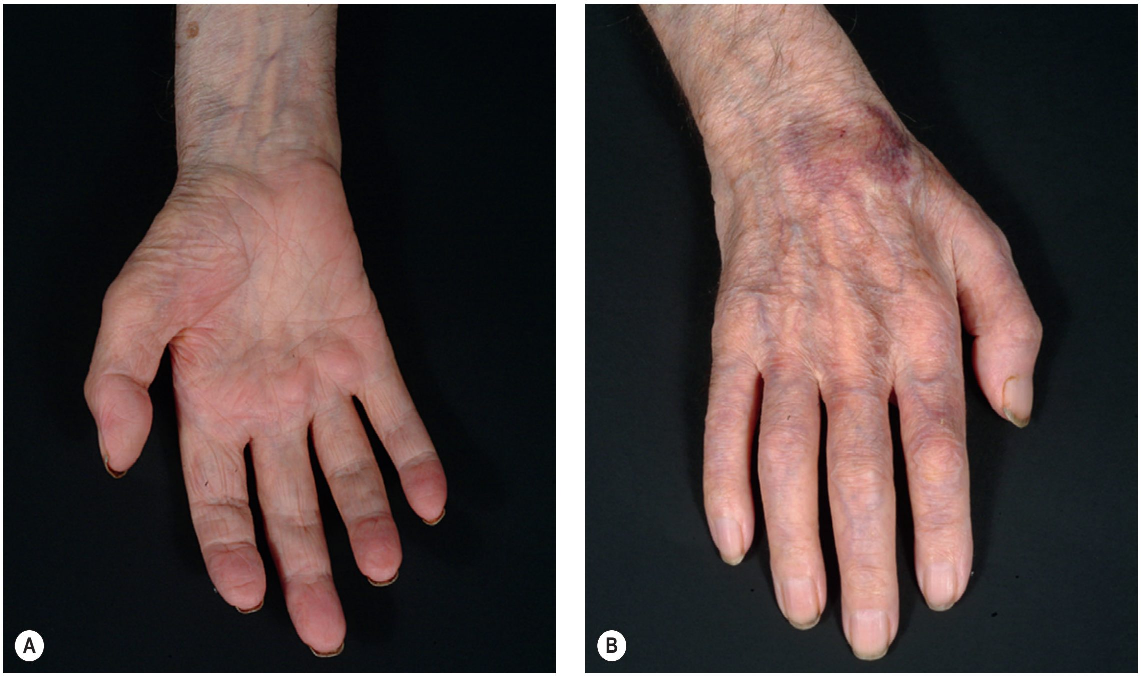


Figure 3.91 (A, B) Wasting of the small muscles of the hand (in multifocal motor neuropathy).

Interpretation

Confirm the diagnosis

Signs may be similar to those of an ulnar nerve lesion but with additional thenar wasting.

What to do next – consider causes

Causes can be considered under the following headings:

- T1 radiculopathy or plexopathy involving T1
- Concurrent median **and** ulnar nerve lesions
- Polyneuropathy (if bilateral and with motor predominance)
- Disuse atrophy (bilateral / asymmetrical), e.g. longstanding rheumatoid arthritis.

If wasting is unilateral it can be hard to know whether you are looking at a radiculopathy, an ulnar nerve lesion or even a median nerve lesion. A quick way of tackling this is to focus on testing the two muscles in Box 3.55.

Consider severity / decompensation / complications

This rather depends upon the cause. A diffuse cause such as motor neurone disease can be overlooked in early stages, often dismissed as a minor mononeuropathy.

Consider function

Tell the examiners how you think it might affect the patient's life, with particular regard to fine tasks.

Box 3.55 **Testing just two muscles can yield much information!**

Abductor pollicis brevis (APB) – median nerve

'Let your palm face the ceiling; now point your thumb up towards the ceiling; don't let me push it down'

First dorsal interosseous (1st DI) – ulnar nerve

'Push your index finger out against my hand'

The little finger may be tested (abductor digitorum minimi) instead of the index finger (1st DI) to assess ulnar nerve integrity

Interpretation

- APB weak + 1st DI weak = T1 radiculopathy
- APB weak + 1st DI spared = median nerve lesion
- APB spared + 1st DI weak = ulnar nerve lesion

Discussion

List some causes of a C8 / T1 root lesion

- Cervical spondylosis
- Syringomyelia (may be bilateral)
- Motor neurone disease
- Pancoast's tumour
- Cervical rib

CASE 3.44 COMMON PERONEAL NERVE LESION

Instruction

Please examine this patient's lower limbs and discuss your findings.

Recognition

There is *wasting of the lateral muscles of the lower leg*, and *weakness of dorsiflexion and eversion* of the ankle, provoking a foot drop (Fig. 3.92), and weakness of toe extension. There may be sensory loss over the lateral calf and dorsum of the foot, but in practice it tends to be slight.

Interpretation

Confirm the diagnosis

Check the ankle reflex. It should be intact. The sciatic nerve has two branches: the common peroneal and tibial nerves. The ankle reflex is conveyed through the S1 root via the tibial nerve, and thus is spared in a peroneal nerve lesion. An absent ankle reflex indicates one of three possible lesions (Box 3.56).

What to do next – consider causes

Consider all causes of a foot drop (Box 3.57).

Consider severity / decompensation / complications

This rather depends upon the cause (Table 3.53).

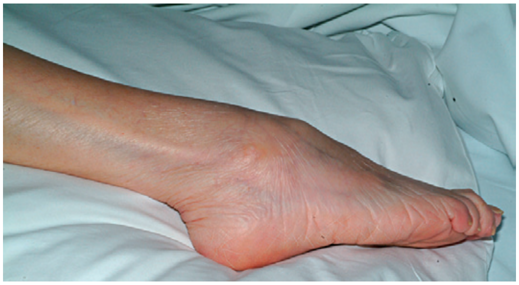


Figure 3.92 Foot drop.

Box 3.56 Causes of an absent ankle reflex

- S1 radiculopathy (by far the commonest cause)
- Complete sciatic nerve lesion
- Tibial nerve lesion (much rarer than lesions of the common peroneal nerve or its deep and superficial divisions)

Consider function

Observe gait. A common peroneal nerve lesion causes a foot drop, resulting in a high stepping gait. Correcting callipers may be at the bedside.

Discussion

What is the nerve root supply to the common peroneal nerve?

See Table 3.53.

Which muscles are supplied by the common peroneal nerve?

See Table 3.53.

Which common sites are affected in a common peroneal nerve palsy?

See Table 3.53.

How would you recognise a sciatic nerve lesion?

This is a less common mononeuropathy in the leg, the site of damage the pelvis, buttock or thigh, and is usually due

Table 3.53 The peroneal nerve

Roots supplying the common peroneal nerve	Muscles supplied by these roots	Common sites of a common peroneal nerve lesion
L4, L5 (mostly L5)	Dorsiflexors – tibialis anterior (deep peroneal branch of common peroneal nerve)	Most commonly compression (plaster casts, leg crossing) or trauma at the fibula neck – the nerve twines around this Diffuse lesions, e.g. diabetes mellitus, vasculitis, leprosy
L5, S1	Evertors – peroneus longus, peroneus brevis (superficial peroneal branch of common peroneal nerve)	

Box 3.57 Causes of foot drop

- Common peroneal nerve lesion
- Sciatic nerve lesion
- L4, 5 (especially 5) radiculopathy (prolapsed lumbar disc)
- Polyneuropathy, especially hereditary sensory and motor neuropathy / Charcot–Marie–Tooth disease
- Upper motor neuron lesion (spinal cord or cortex)

Preserved inversion strongly suggests a common peroneal nerve lesion; any weakness of inversion indicates a more proximal lesion.

to trauma, buttock compression or tumour. It causes weakness in the hamstrings plus common peroneal and tibial nerve deficits and sensory loss over areas of the posterior cutaneous nerve of the thigh plus the common peroneal and tibial nerves. The differential diagnosis is a radiculopathy of L5 or S1.

How would you recognise a femoral nerve lesion?

This is a less common mononeuropathy in the leg, usually due to a psoas haematoma or trauma. It causes weakness of hip flexion and knee extension and sensory loss over the anterior thigh and medial calf. The differential diagnosis is a radiculopathy of L3 or L4, or diabetic amyotrophy.

What is diabetic amyotrophy?

This refers to pain, weakness and wasting in one or both quadriceps in diabetes mellitus, probably due to lumbosacral plexus microvasculitis.

How would you recognise an obturator nerve lesion?

This is a rare mononeuropathy, usually due to a pelvic tumour or surgery. It causes weakness of hip adduction and sensory loss over the medial thigh. The differential diagnosis is a lumbosacral plexopathy.

How would you recognise a lesion of the lateral cutaneous nerve of the thigh or 'meralgia paraesthetica'?

This is a common mononeuropathy in the leg, the site of damage often the inguinal ligament and commonly due to obesity, pregnancy or surgery. It causes sensory disturbance, often pain or tingling, at the lateral mid-thigh, without weakness. The differential diagnosis is a radiculopathy of L2.

CASE 3.45 PERIPHERAL NEUROPATHY

Instruction

Please examine this patient's legs and discuss your findings.

Recognition

There may be *symmetrical impairment of sensation to all modalities in a stocking (and sometimes also glove) distribution* (Fig. 3.93) There may be *distal wasting* and *weakness* and *distal areflexia*.

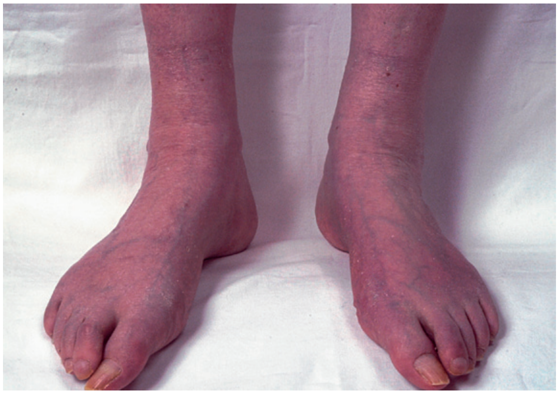


Figure 3.93 Stocking distribution.

Box 3.58 **Autonomic symptoms**

- Postural hypotension
- Atonic bladder
- Constipation
- Erectile dysfunction
- Dry eyes and mouth
- Anhidrosis
- Paroxysmal hypertension, tachycardia or bradycardia (rare)
- Hyperhidrosis (rare)
- Diarrhoea (rare)

Interpretation

Confirm the diagnosis

The classic picture of stocking sensory loss and/or distal wasting, weakness and diminished reflexes due to a distal symmetrical polyneuropathy is likely (Box 3.61).

What to do next – consider causes/assess other systems

Look for punched-out foot ulcers suggesting diabetic neuropathy. Tell the examiners you would:

- Take a history for systemic disease (especially diabetes, chronic kidney and liver disease), infection (tick bites for Lyme disease, human immunodeficiency virus (HIV)) and malignancy
- Take a drug and possible toxin exposure history
- Take a family history (inherited neuropathies, shared toxin exposure).

Diabetes is the most common cause in the developed world and, globally, leprosy remains a common cause. Other common causes include metabolic disorders, infection, vasculitis, drugs and toxins. Dysimmune and inherited polyneuropathies are not uncommon chronic causes.

Tell the examiners you would ask about sensory and motor symptoms, and autonomic symptoms (Box 3.58).

Box 3.59 **Definitions of sensory symptoms**

- Paraesthesia – abnormal sensations evoked or spontaneous and not unduly painful or unpleasant
- Dysaesthesia – unpleasant paraesthesia
- Hyperaesthesia – increased sensitivity to a stimulus
- Allodynia – painful sensation resulting from a non-painful stimulus, e.g. light touch

Autonomic symptoms occur mostly in generalised polyneuropathy, e.g. diabetes polyneuropathy, Guillain–Barré syndrome, porphyria and amyloid neuropathy; rarely, they occur as a pandysautonomia, presumably with a dysimmune basis.

Consider severity / decompensation/ complications

If there is a predominant symmetrical motor neuropathy, tell the examiners you would immediately attempt to exclude Guillain–Barré syndrome (Case 3.47), which can cause acute severe ascending paralysis involving the arms, chest, neck and cranial nerves (facial and bulbar weakness), and respiratory failure.

Consider function

Tell the examiners you would ask about sensory symptoms (Box 3.59) and the limitations posed by weakness and gait disturbance. Motor tasks requiring manual dexterity are often impaired.

Discussion

What is meant by the term peripheral neuropathy?

It is a general term for any disorder of the peripheral nervous system. The causes are disparate and the presentation is variable. Most can be categorised by subtype and cause through a logical and sequential approach using clinical findings, electrodiagnostic and laboratory tests, with implications for management and prognosis.

How common is peripheral neuropathy?

It is common, with an overall prevalence of 2.4% of the population rising to 8% over 55 years.

How would you further evaluate a peripheral neuropathy?

This requires clinical evaluation, electrodiagnostic studies and laboratory tests.

Clinical evaluation and electrodiagnostic studies

The clinical manifestations vary widely, with varying combinations of sensory symptoms, pain, muscle weakness or atrophy, and autonomic symptoms. Electrodiagnostic studies, including nerve conduction studies and needle electromyography, should be considered whenever peripheral neuropathy is suspected. A nerve conduction study involves electrical stimulation of a peripheral nerve and recording, further along that nerve, the latency and amplitude of the action potential. From the latency, a conduction velocity may be calculated; normal is 50–60 m/s in the arm and 40–50 m/s in the leg. Amplitude is normally small for small nerves and large for larger compound muscle action potentials. In demyelinating neuropathies, the velocity is slowed but the amplitude is preserved. The opposite is characteristic of axonal neuropathies. Although some investigate for common causes before using electrophysiological tests, evidence does not support this and many neurologists consider it a mandatory extension of neurological examination. The most important details to determine are outlined in Table 3.54. An overview of evaluation of peripheral neuropathy is shown in Figure 3.94.

Table 3.54 Important details to determine from clinical evaluation and electrophysiological tests

Rate of development and duration	Acute (up to 4 weeks)
	Subcute (4–8 weeks)
	Chronic (> 8 weeks)
Pattern of progression	Gradual progression
	Relapsing–remitting
Pattern of distribution	Mononeuropathy
	Mononeuropathy multiplex
	Plexopathy
	Polyneuropathy
Pattern of symptoms	Predominantly motor
	Predominantly sensory
	Both
Pattern of fibre involvement	Most polyneuropathies involve large and small fibres
	Weakness or wasting indicates large-fibre involvement since all motor fibres except gamma efferents to muscle spindles are large
	Sensory ataxia or areflexia indicates large-sensory-fibre involvement since vibration, proprioception and reflex afferent fibres are large
	Positive sensory symptoms such as pain and burning dysaesthesias indicate small-fibre involvement since pain and temperature sensibilty and peripheral autonomic functions rely on small fibres; causes incude diabetes, amyloidosis and human immunodeficiency virus
Electrophysiological type	Mainly demyelinating
	Mainly axonal

What is meant by the term mononeuropathy?

This refers to a lesion of a single peripheral nerve. Typical causes are outlined in Table 3.55.

There are essentially three types of focal peripheral nerve lesion:

- *Neuropraxia*, focal or segmental demyelination with preservation of the axon and recovery in 2–12 weeks
- *Axonotmesis*, in which the axon is divided but the epineurium remains intact and regrowth occurs at 1 mm/day from the injured site
- *Neurotmesis*, where the nerve is divided and no longer in continuity, with no recovery.

These can occur together, appreciated clinically when relatively rapid neuropraxic recovery is followed by slower axonotmesis recovery.

What are the common mononeuropathies and how are they diagnosed?

Diagnosis of mononeuropathies depends on recognising that the neurological deficit involves the distribution of a single nerve. This requires knowledge of anatomy and of the motor and sensory territories of nerves, but fortunately relatively few nerves are prone to mononeuropathies, notably:

- Median nerve compression in carpal tunnel syndrome (the commonest)
- Ulnar nerve compression at the elbow (the next most common)
- Radial nerve lesion after acute compression ('Saturday night' palsy)
- Common peroneal nerve lesion.

Peripheral nerves are arranged in fascicles so that a more proximal lesion may be mistaken for a more distal one, e.g. a foot drop following hip replacement with weak eversion and preserved inversion and sensory loss in the common peroneal nerve distribution is almost certainly a sciatic nerve lesion involving the common peroneal fascicle rather than a more distal common peroneal nerve lesion. Electrodiagnostic studies help localise, determine severity and exclude unsuspected mononeuropathy multiplex. Multiple compression mononeuropathies are often part of the spectrum of hereditary neuropathy with liability to pressure palsies.

Table 3.55 Causes of a mononeuropathy

External insult (acute or insidious onset as in repeated minor external compression such as habitual leaning on the elbow for ulnar lesion or kneeling for common peroneal lesion)	Direct trauma, including prolonged external compression, e.g. coma
	Repeated minor trauma
	Traction
	Injection
	Cold, burns, radiation
Internal entrapment or compression (usually insidious onset)	Median nerve entrapment in carpal tunnel
	Ulnar nerve entrapment at elbow
	Rarely, compression by tumours or vascular malformations
Intrinsic lesion (usually acute onset)	Infarct, usually a focal manifestation of a generalised process, e.g. vasculitis, conduction block in multifocal motor neuropathy
Increased susceptibility to injury (usually insidious onset)	e.g. diabetes, alcohol, nutritional deficiency, hereditary liability to pressure palsies, combined with minor compression or entrapment

What is meant by the term mononeuropathy multiplex?

This refers to involvement of multiple separate non-contiguous peripheral nerves, either simultaneously or serially. The pattern of nerve involvement is random, multifocal and often evolves quickly, sometimes progressing to a summation of nerve lesions with confluent, symmetric deficits mimicking a distal symmetrical polyneuropathy. The early pattern of onset is important. Urgent assessment is important because vasculitis is a common cause; it is usually systemic but may be confined to the peripheral nerves. Common causes of mononeuropathy multiplex are listed in Box 3.60.

Sural or superficial peroneal nerve biopsy may be helpful unless the diagnosis is clear, as in diabetic amyotrophy, or a systemic cause has been identified.

What types of polyneuropathy are there clinically?

The most common variety is distal symmetrical polyneuropathy; nerve fibres are affected in a length-dependent manner, length meaning distance from the parent nerve cell body (either the dorsal root ganglion sensory neuron or the anterior horn motor neuron), irrespective of root or nerve trunk distribution. The typical progression of symptoms and signs is outlined in Box 3.61.

What are the causes of distal symmetrical polyneuropathy?

This pattern is associated with many systemic diseases, metabolic disorders, infections, malignancies, drugs and toxins (Table 3.56), the main causes being diabetes, alcohol misuse, and HIV infection, but vitamin B12 deficiency, uraemia, paraproteinaemia and hypothyroidism are also common.

How are polyneuropathies classified on the basis of nerve conduction studies?

Polyneuropathies are most practically subtyped as acute, chronic demyelinating or chronic axonal.

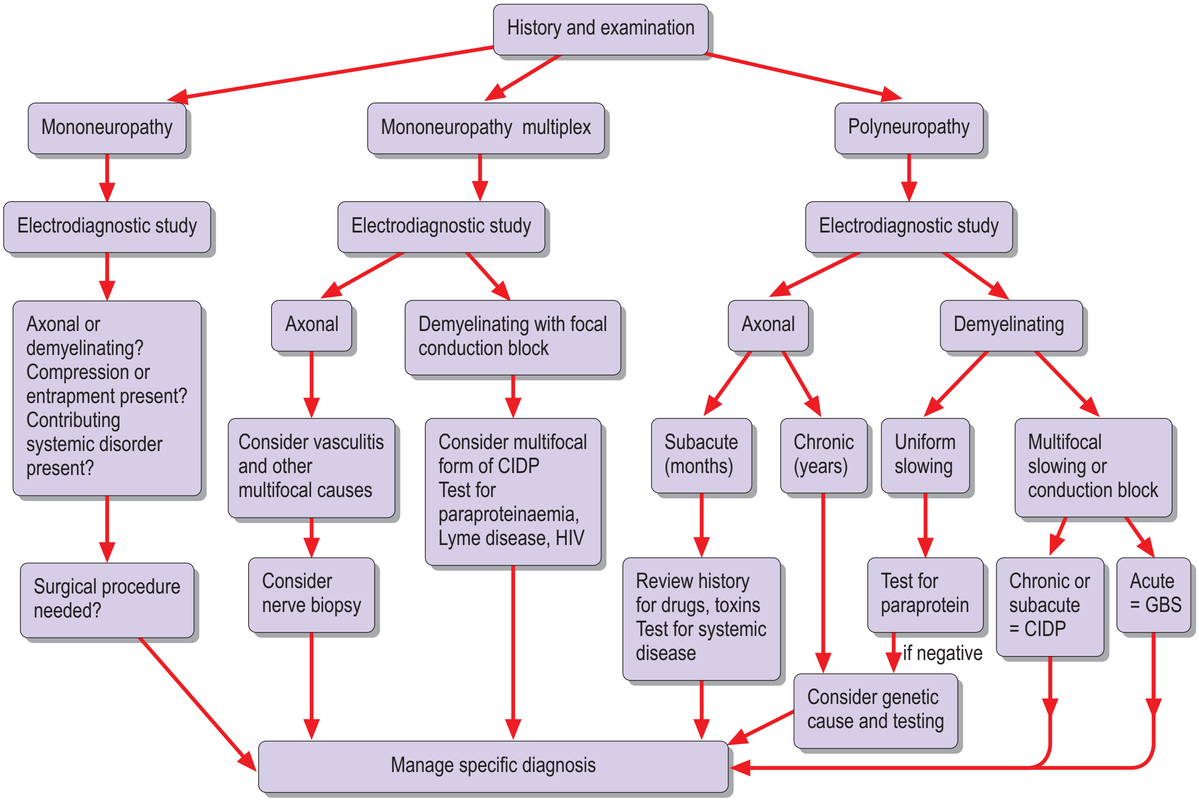

History and examination
Mononeuropathy
Mononeuropathy multiplex
Polyneuropathy
Electrodiagnostic study
Electrodiagnostic study
Electrodiagnostic study
Axonal or demyelinating? Compression or entrapment present? Contributing systemic disorder present?
Axonal
Demyelinating with focal conduction block
Axonal
Demyelinating
Consider vasculitis and other multifocal causes
Consider multifocal form of CIDP Test for paraproteinaemia, Lyme disease, HIV
Subacute (months)
Chronic (years)
Uniform slowing
Multifocal slowing or conduction block
Surgical procedure needed?
Consider nerve biopsy
Review history for drugs, toxins Test for systemic disease
Test for paraprotein
Chronic or subacute = CIDP
Acute = GBS
if negative
Consider genetic cause and testing
Manage specific diagnosis

Figure 3.94 Evaluation of peripheral neuropathies. CIPD, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain–Barré syndrome; HIV, human immunodeficiency virus.

Box 3.60 **Common causes of mononeuropathy multiplex**

Axonal

- Vasculitis, e.g. Churg–Strauss syndrome, connective tissue disease, e.g. rheumatoid arthritis
- Diabetic amyotrophy (acute pain in thigh, probably due to vasculitis in lumbosacral plexus)
- Leprosy
- Lyme disease
- Human immunodeficiency virus
- Carcinoma
- Lymphoma
- Sarcoidosis
- Amyloidosis
- Cryoglobulinaemia

Demyelinating

- Chronic inflammatory demyelinating polyradiculopathy or variant, e.g. multifocal motor neuropathy
- Multifocal neuropathy with liability to pressure palsies (deletion in *PMP22* gene)

Box 3.61 **Typical progression of symptoms and signs in distal symmetrical polyneuropathy**

- Distal, symmetrical sensory symptoms (numbness, burning, paraesthesia or dysaesthesia of toes or feet); weakness sometimes comes first, of toe and foot dorsiflexion
- Ascending sensory symptoms, weakness of toe and foot dorsiflexion (unable to stand on heels) and depression or loss of ankle reflexes
- Plantar flexion remains relatively strong (able to stand on toes)
- Shin and fingertip sensory symptoms
- Gait disorder – proprioceptive loss and extensor muscle weakness
- Mid-thigh, upper forearm and lower abdominal sensory symptoms – a triangular-shaped area of hypoaesthesia with its apex in the midline; may ascend as far as umbilicus or even manubriosternum (unlike a spinal cord lesion, with sensory loss at front and back)
- Advanced polyneuropathy with stocking-glove diffuse sensory loss, distal muscle wasting and weakness and absent reflexes

Table 3.56 Causes of polyneuropathy

Causes		Sensory (S)/ motor (M)/ sensorimotor (SM)	Axonal (A)/ demyelinating (D)	Notes
Systemic disease and metabolic	Diabetes mellitus	S, SM, rarely M	A and D	Commonest cause of chronic polyneuropathy Glucose intolerance commonly produces small-fibre polyneuropathy with a burning feet sensation without numbness and with preserved reflexes, and nerve conduction studies are normal (thermal thresholds and other quantitative sensory tests are abnormal and skin biopsy can be diagnostic)
	Chronic kidney disease/uraemia	SM	A	Common Controlled with dialysis and cured by transplant
	Chronic liver disease	S or SM	A and D	Mild
	B12 deficiency	S	A	Common Myelopathy may dominate
	Nutritional deficiency – B vitamins, thiamine, folic acid, often alcoholism	SM	A	
	Hypothyroidism	S	A	Increasingly recognised as common
	Malabsorption, e.g. inflammatory bowel disease, coeliac disease	S or SM	A	Not necessarily vitamin deficiency, possible immune basis
	Porphyria (rare)	M or SM	A	Often acute, often proximal and upper limbs Differential diagnosis GBS
	Sarcoidosis	S or SM	A	Polyneuropathy or mononeuropathy multiplex Facial neuropathy common
	Primary systemic amyloidosis (rare)	SM	A	Most associated with paraproteinaemia (myeloma, Waldenström's macroglobulinaemia, lymphoproliferative disease)
	COPD (rare)	S or SM	A	Severe COPD
Infection	Leprosy	S > SM	A	Cutaneous nerves
	Lyme disease	S > M	A	Focal or multifocal radiculoneuropathy Facial nerve neuropathy
	HIV	S > M	A	Common Chronic distal sensory polyneuropathy Other types in early infection

Table 3.56 Causes of polyneuropathy—cont'd

Causes		Sensory (S)/ motor (M)/ sensorimotor (SM)	Axonal (A)/ demyelinating (D)	Notes
Malignancy	Carcinoma	SM Pure S (rare)	A	Lung cancer Paraneoplastic ganglionitis with small cell or breast cancer
	Lymphoma	SM	A > D	
	Paraproteinaemia (monoclonal gammopathy of uncertain significance, multiple myeloma)	S, M or SM	A	Common
	Osteosclerotic myeloma Plasmacytoma	SM	D	Association with POEMS syndrome – polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes
Drugs	Amiodarone Antibiotics, e.g. chloramphenicol, chloroquine, dapsone, ethambutol, isoniazid, metronidazole, nitrofurantoin, nucleoside antiretrovirals Bortezomib Chemotherapuetic, e.g platinum, taxol, vincristine Colchicine Gold Hydralazine Nitrous oxide Phenytoin Podophyllin Pyridoxine (vitamin B6) Suramin Thalidomide	S, M, SM	Usually A	
Toxins	Alcohol	SM	A	Common
	Arsenic	SM	A or D	Painful sensory symptoms then weakness, systemic illness e.g. genitourinary symptoms, Mees lines on nails Differential diagnosis GBS
	Carbon disulphide (Cellophane manufacturing)	S > M	A	Sensory then motor symptoms
	Diphtheria toxin	SM	D	Rare, 8–12 weeks after infection
	Hexacarbons (gasoline or glue)	SM	A and D	May be severe
	Lead	M	A	Wrist drop Differential diagnosis GBS
	Mercury	M > S	A	Differential diagnosis GBS
	Organophosphates (insecticides)	M > S	A	10–20 days after exposure
	Thallium (rodenticides)	S > M	A	Differential diagnosis GBS
Inherited neuropathies	Charcot–Marie–Tooth disease types 1, 4 and X1	SM	D	
	Hereditary liability to pressure palsies	SM	D	

COPD, chronic obstructive pulmonary disease; GBS, Guillain–Barré syndrome; HIV, human immunodeficiency virus.

Acute polyneuropathy

Guillain–Barré syndrome and the differential diagnosis of acute neuropathy are discussed in Case 3.47.

Chronic polyneuropathy

Chronic symmetrical polyneuropathy is the commonest type of polyneuropathy, and differential diagnosis is usually narrowed down through history, examination and electrodiagnostic studies to a few possibilities. For example, a chronic, steadily progressive distal symmetrical sensorimotor polyneuropathy with predominantly axonal features is most likely to be the result of systemic or metabolic disease, drugs or toxins; a longstanding chronic, predominantly motor distal symmetrical polyneuropathy with uniformly demyelinating features is most likely an inherited polyneuropathy, e.g. Charcot–Marie–Tooth type 1; acquired mimics, e.g. chronic inflammatory demyelinating poly(radiculo)neuropathy (CIDP) or paraproteinaemia are excluded by electrodiagnostic studies and electrophoresis.

■ **Chronic demyelinating polyneuropathy.** The causes are limited. Genetic causes include Charcot–Marie–Tooth disease type 1, 4 or X1, hereditary liability to pressure palsies, metachromatic leucodystrophy, globoid cell leucodystrophy and Refsum's disease. Acquired causes include CIDP, multifocal motor neuropathy (MMN) and paraproteinaemic demyelinating polyneuropathy (associated with antibodies to myelin-associated glycoprotein), monoclonal gammopathy of uncertain significance and osteosclerotic myeloma. Acquired causes are mostly immunologically mediated. CIDP is the most common type, either gradually progressive or relapsing. It is usually, but not always, predominantly motor, causing proximal as well as distal weakness. Cerebrospinal protein concentration tends to be very high. MMN, related to CIDP, produces partial conduction block and is restricted to motor axons, usually producing weakness and atrophy in the hands and forearms. Around 10% of acquired causes are due to paraproteinaemias, usually producing slowly evolving distal symmetrical sensory abnormalities in the feet.

■ **Chronic axonal polyneuropathy.** This is the commonest type of polyneuropathy and there are many causes (Table 3.56). Several varieties of hereditary neuropathy, especially axonal types of Charcot–Marie–Tooth disease (CMT2), present with this pattern. No cause is found in up to 25% of patients. Proof of diagnosis can be made on unmyelinated nerve fibre density in a skin biopsy, but this is seldom available. Most idiopathic distal symmetrical polyneuropathies progress slowly and seldom produce overt disability and treatment of sensory symptoms is paramount.

What laboratory and other tests would you consider in the investigation of peripheral neuropathy?

These are outlined in Table 3.57.

What is the role of a nerve biopsy in peripheral neuropathy?

Nerve biopsy is useful in documenting inflammatory disorders such as vasculitis, sarcoidosis, CIDP, infectious diseases such as leprosy, or infiltrative disorders such as amyloidosis or tumour. It is usually reserved for cases when diagnosis cannot be reached by other means.

What are the principles of treatment in peripheral neuropathy?

These can be divided into specific and general approaches.

Specific

Treatments specific to the subtype include removal of any exogenous cause or treatment of any medical cause. CIDP and MMN can respond to immunotherapy, both respond to intravenous immunoglobulin, but only CIDP responds to corticosteroids and plasma exchange; some patients with MMN have deteriorated with steroids.

General

Foot care, ankle supports and physiotherapy can be useful. Painful peripheral neuropathy is difficult to treat. The most useful agents are anticonvulsants (especially gabapentin and carbamazepine) and tricyclic antidepressants (especially amitriptyline).

What do you know about the mechanism of neuropathic pain?

Most pain is known as nocioceptive or inflammatory pain in which a stimulus, usually tissue injury, sends impulses to the cortex along thinly myelinated Aδ or unmyelinated C fibres. Inflammatory mediators sensitise nociceptors such that further trivial stimuli produce pain disproportionate to the applied stimulus (primary hyperalgesia) or to a usually non-painful stimulus (allodynia), perhaps warning the brain that the area should be protected. Neuropathic pain is different. Disruption of the normal mechanisms in pain transmission lead to pain even without stimulus and may be an aberrant response to previous but now settled inflammation or arise *de novo* in nerves. Aberrant mechanisms may include: inflammation sensitising uninjured nerves; proliferation of sodium channels leading to hyperexcitability; demyelination provoking sensitisation; sympathetic proliferation; aberrant termination of β-fibres and enhancement of the receptive field at the dorsal horn; ischaemia or trauma centrally; and loss of diffuse noxious inhibitory control leading to abnormal gating of pain transmission in the spinal cord.

Give some examples of neuropathic pain

Painful diabetic neuropathy

This is a distal, symmetrical sensorimotor polyneuropathy that is often painful, and may occur with impaired glucose tolerance before diabetes emerges. Tactile allodynia and mechanical and thermal hyperalgesia are common, and hypoalgesia may develop as disease develops.

Table 3.57 Laboratory and other tests in peripheral neuropathy

Initial tests	Haematology	Full blood count
		Inflammatory markers
		B12
		Folate
	Biochemistry	Fasting blood glucose or oral glucose tolerance test
		Renal function
		Liver function
		Calcium
		Thyroid function
		Protein electrophoresis and immunoglobulins
	Autoimmune profile	ANA and rheumatoid factor
		ENA for Sjögren's syndrome and SLE
		ANCA for vasculitis
		Cryoglobulins
	Urine	Glucose
		Protein
	Radiology	Chest X-ray
More specialised tests for specific causes	Systemic/metabolic	Serum (+/− cerebrospinal fluid) ACE
		Coeliac disease antibodies
		Porphyrins in blood, urine or stool
	Infection	Lyme serology
		HIV testing
		Campylobacter jejuni, cytomegalovirus, hepatitis B and C, and herpes virus serology
	Malignancy	Mammography
		Skeletal survey
		CT thorax, abdomen, pelvis (TAP)
		Antineuronal antibodies
	Drugs and toxins	Heavy metal toxicity from blood, urine, hair or nail analysis
	Dysimmune	Anti-ganglioside antibody profile (GM1, MMN with conduction block; other, see Case 3.47 Guillain–Barré syndrome)
		Anti-myelin associated glycoprotein antibodies (IgM paraproteinameic neuropathy)
		Cerebrospinal fluid analysis including Ig oligoclonal bands
	Inherited	Tailored to clinical profile, e.g. chromosome 17 (duplication for Charcot–Marie–Tooth disease type 1a, deletion for hereditary neuropathy with liability to pressure palsies), familial amyloid polyneuropathy

ACE, angiotensin-converting enzyme; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibody; CT, computed tomography scan; ENA, extractable nuclear antigens; HIV, human immunodeficiency virus; Ig, immunoglobulin; MMN, multifocal motor neuropathy; SLE, systemic lupus erythematosus.

Sciatica

Sciatica is an outdated word and is typically compressive root pain. However, many people with sciatica symptoms do not have compressive disease and symptoms may be due to inflammatory mediator release.

Thigh pain

Magnetic resonance spinal imaging might be performed to exclude spinal stenosis or radiculopathy in patients with refractory symptoms and a not unequivocal diagnosis. The differential diagnosis of thigh pain, for example, includes femoral neuropathy, diabetic amyotrophy or meralgia paraesthetica.

Trigeminal neuralgia

This is typically a severe, shock-like, paroxysmal hemifacial pain, often induced by shaving or brushing teeth. Imaging should be undertaken to exclude cerebellopontine angle tumours or multiple sclerosis. Vascular compression of the trigeminal ganglion is common.

Post-herpetic neuralgia

This is a consequence of previous inflammation from herpes zoster.

Central post-stroke pain

This remains poorly understood and evidence-based.

How might you treat patients with neuropathic pain?

A stepwise approach should start with tricyclics if not contraindicated (amitriptyline, sedating alternatives including imipramine or lofepramine).

Anticonvulsants gabapentin or pregabalin are used if tricylics are contraindicated or ineffective.

Carbamazepine is an alternative but ataxia is a common side effect. Carbamazepine or oxcarbazepine may be useful in trigeminal neuralgia where surgical decompression is not possible.

Serotonin and norepinephrine (noradrenaline) reuptake inhibitors may be useful.

Referral to a pain clinic for consideration of intrathecal or local anaesthetic techniques or infusions might be a next step, or consideration of opioid analgesia.

Topiramate at a dose of 25 mg once or twice daily has been used with some effect, but by this stage the law is generally that of diminishing returns and acupuncture is sometimes tried. Some patients are helped by clonazepam, but this is rather sedating, others by ketamine or cannabinoids with increasing concern about drug-related harm and dependency.

CASE 3.46 CHARCOT–MARIE–TOOTH DISEASE AND HEREDITARY NEUROPATHIES

Instruction

Please examine this patient's legs and discuss your findings.

Recognition

A severe, predominantly motor, peripheral neuropathy with marked wasting (causing distal narrowing or *inverted champagne bottle legs*) may be caused by *hereditary sensory and motor neuropathy* (HSMN) (Fig. 3.95). There may also be *clawing of the toes* and *pes cavus* with marked weakness of dorsiflexion. Thickened nerves and tremor are sometimes present.

Interpretation

Confirm the diagnosis

In pes cavus, the arch of the foot is high, the foot shortened with bunched up, clawed toes, and its lateral border does not contact the ground. Foot drop usually develops later.

What to do next – consider causes

CMT-1

Of CMT-1 (HMSN type 1), 70–80% are caused by duplication in the *PMP22* gene (probably encoding myelin protein) on chromosome 17. The phenotype is highly variable, ranging from the classic picture with pes cavus and 'stork legs' (severe distal wasting or 'inverted champagne bottle legs') to minimal deficit with almost undetectable clawing of the toes. Different mutations can cause a similar phenotype, and classification relies on genetic testing, now widely available.

CMT-2

CMT-2 (HSMN type 2) accounts for one-third of dominantly inherited neuropathies and is also clinically heterogeneous, but often only becomes detectable in later life.

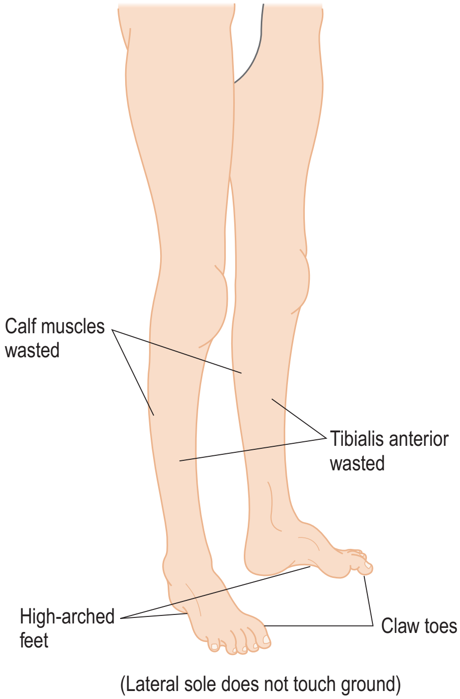


Figure 3.95 Hereditary sensory and motor neuropathy type 1.

Consider severity/ decompensation/ complications

The neuropathy often ascends relentlessly to cause wasting of the intrinsic muscles of the hands, whilst sensory impairment is usually minimal or absent.

Consider function

If you suspect HSMN a marked bilateral high-stepping gait due to bilateral foot drop is likely; this is predominantly due to bilateral common peroneal nerve palsy, these nerves being especially vulnerable in this condition and often thickened.

Discussion

What hereditary neuropathies do you know of?

The hereditary neuropathies are a complex and heterogeneous group of disorders with an estimated prevalence of 1–3/ 10 000. Many genes and linkage sites have been described. Most are extremely rare. The most common are dominantly inherited Charcot–Marie–Tooth (CMT) disease, also known as HSMN types 1 (demyelinating) and 2 (axonal), and X-linked CMT (CMT-X). Spontaneous mutations also occur. CMT disease was once known as 'peroneal muscle atrophy'. Other hereditary neuropathies, and of chronic demyelinating polyneuropathy type, are CMT type 4, hereditary liability to pressure palsies, metachromatic leucodystrophy, globoid cell leucodystrophy and Refsum's disease.

CASE 3.47 GUILLAIN–BARRÉ SYNDROME

Instruction

Please examine this patient's lower limbs and discuss your findings.

Recognition

There is *symmetrical weakness in an ascending distribution with areflexia*.

Interpretation

Confirm the diagnosis

Guillain–Barré syndrome (GBS) is an acute (typically < 4 weeks), predominantly motor, distal but rapidly ascending, symmetrical polyneuropathy. It often starts with mild extremity weakness or distal paraesthesia, which is easy to dismiss; ultimately there is global (distal and proximal) weakness, as compared with dying-back axonopathies (e.g. alcohol, toxin-related), which are usually distal. Areflexia is characteristic but may not occur in the first few hours. Contrary to what is often written, sensory symptoms do occur typically, although they are often mild and seldom produce signs. GBS does not usually cause visual failure, hearing loss or early sphincter involvement. Diagnosis is often clinical, supported by examination of cerebrospinal fluid and neurophysiological studies.

What to do next – consider causes

Mention a differential diagnosis of acute flaccid paralysis to the examiners (Box 3.62). In clinical practice you would try to identify if there is sensory, cranial nerve, respiratory, bladder and bowel, or autonomic nervous system involvement to help discriminate the possibilities.

GBS has numerous subtypes (Table 3.58) and is arbitrarily defined by an onset lasting up to 4 weeks. Subacute inflammatory demyelinating polyradiculoneuropathy and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are defined by 4–8 weeks and over 8 weeks, respectively. Some patients with GBS have recurrent peaks of symptoms within an apparent single but protracted episode of illness and then it may be difficult to distinguish from CIDP; indeed, the two conditions may overlap.

Consider severity / decompensation / complications

Progression is often swift and life-threatening respiratory muscle paralysis can occur. A quarter to a third of patients need ventilatory support. Tell the examiners that you would arrange regular spirometry and vital capacity. A falling vital capacity is a more useful warning sign of incipient respiratory failure (< 20 ml / kg most at risk) than blood gases or oximetry, which may be preserved until breathing stops!

Consider function

Patients have flaccid paralysis of the lower limbs especially and cannot walk. Complete or near-complete recovery, while likely, is not assured.

Discussion

How common is GBS?

The incidence is 1–2 cases per 100 000, with relative uniformity between countries, although it may be more common where infectious causes are common. It is the commonest cause of acute neuromuscular paralysis. The male–female ratio is 0.8 : 1, the incidence rises with age, and there is a slight bimodal distribution.

What causes GBS?

GBS is not a single disease but has various subtypes. There is no single cause, and the cause is often unknown, but infections that are known to trigger forms of GBS include *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, *Mycoplasma pneumoniae* and human immunodeficiency virus; 75% of patients have a preceding infection, usually respiratory or gastrointestinal.

Box 3.62 **Differential diagnosis of acute flaccid paralysis**

Brainstem disease

- Brainstem stroke
- Brainstem encephalitis (including paraneoplastic)

Acute myelopathy

- Acute transverse myelitis
- Space-occupying lesion
- Japanese encephalitis
- West Nile virus
- Enterovirus 71

Anterior horn cell disease

- Poliomyelitis or other neurotropic virus; other infections causing acute flaccid paralysis include West Nile virus, human immunodeficiency virus and brucellosis

Peripheral neuropathy

- Guillain–Barré syndrome
- Diphtheritic neuropathy
- Botulinum neuropathy
- Lyme disease
- Toxins, e.g. venoms: snake, spider, fish, shellfish, tick, botulism; chemicals: arsenic, lead, thallium, organophosphates; drugs: lithium, gold, nitrofurantoin
- Acute intermittent porphyria
- Vasculitis neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy
- Rabies or post-rabies vaccine neuropathy
- Vitamin B1 deficiency (beri beri)

Neuromuscular junction disease

- Myasthenic disorders, e.g. myasthenia gravis, Lambert–Eaton myasthenic syndrome, neuromuscular blocking drugs

Myopathy

- Hypokalaemia or other electrolyte disturbance (sodium, potassium, calcium, magnesium, phosphate)
- Hypophosphataemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Periodic paralysis

Non-neurological conditions, e.g. hyperventilation and functional disorders

What is the pathophysiology of GBS?

GBS comprises at least four subtypes of acute peripheral neuropathy.

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

GBS appears to be triggered by infection in most patients, and a third have serological evidence of *C. jejuni* and a few continue to secrete this faecally. The pathophysiology of GBS is likely to be that infectious triggers share epitopes with antigens in peripheral nerve tissue and *C. jejuni* lipopolysaccharide shares epitopes with certain gangliosides, although the serological presence of anti-ganglioside antibodies is more closely observed with other types of GBS than AIDP. The AIDP subtype appears to be mediated by T cells against peptides from myelin proteins PO, P2 and PMP22, although antibodies and complement are also involved.

Axonal subtypes of GBS – acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN)

These are caused by antibodies to gangliosides on the axonomella that target macrophages to invade the axon at the node of Ranvier and cause damage and degeneration; it is likely that the antibodies involved fix complement, which attracts the macrophages. Although T-cell immunity in GBS is not yet clearly understood, many of the antibodies involved are of immunoglobulin G1 (IgG1) or IgG3 subtype which rely on T-cell collaboration. Around a third of patients with GBS have had recent *C. jejuni* infection, and axonal subtypes are especially common in these people. The *Campylobacter* bacterial wall contains ganglioside-like structures and antibodies against it may similarly attack axons in AMAN, in which antibodies to GM1, GM1b, GD1a and Ga1Nac-GD1a are implicated, and ASMAN, in which all of the above, except Ga1Nac-GD1a, are implicated.

Fisher syndrome

This subtype is especially associated with antibodies to GQ1b (90% of patients have this), and similar cross-reactivity with ganglioside structures in *Campylobacter* has been observed.

What are the clinical manifestations of the different types of GBS?

These are described in Table 3.58.

How is GBS diagnosed?

The Asbury and Camblath 1990 WHO-AIREN criteria are sometimes invoked (Box 3.63).

Investigations in GBS are listed in Table 3.59. Investigations serve chiefly to exclude other causes. Electrodiagnostic studies are important in diagnosis, subtype classification and confirmation of peripheral neuropathy. Sufficient data are needed, as described in Table 3.58, and with these data one of three subtypes – AIDP, AMAN, AMSAN – can be identified. However, unlike for clinical criteria, there is no consensus on neurophysiological criteria. Sometimes an ‘inexcitable’ result is obtained, dCMAP absent in all nerves or present in only one nerve with dCMAP < 10%, and then it is not possible to determine whether the absence of recordable action potentials is the result of complete conduction block from demyelination or of axonal

Table 3.58 Features of the different subtypes of Guillain–Barré syndrome

	Features	Antibodies	Neurophysiology
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Most common subtype by far (95% of cases in Europe and North America) Acute weakness of all four limbs with hyporeflexia or areflexia, reaching peak within 4 weeks Can involve cranial nerves Can cause respiratory muscle weakness Autonomic involvement common (e.g. tachycardia, hypertension, lack of sinus arrhythmia), especially if severe respiratory weakness	Unknown	At least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and dCMAP > 10% of LLN: Motor conduction velocity < 90% LLN (85% if dCMAP < 50%) Distal motor latency > 110% ULN (> 120% if dCMAP < 100% LLN) pCMAP / dCMAP ratio < 0.5 and dCMAP > 20% F-response latency > 120% ULN
Acute motor axonal neuropathy (AMAN)	Acute weakness of all four limbs with hyporeflexia or areflexia (but sometimes reflexes retained or brisk in AMAN), reaching peak within 4 weeks Can involve cranial nerves Can cause respiratory muscle weakness Autonomic involvement less common	GM1, GM1b, GD1a, Ga1Nac-GD1a	No features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LLN Sensory action amplitudes normal
Acute motor and sensory axonal neuropathy	Acute weakness and sensory disturbance of all four limbs with hyporeflexia or areflexia, reaching peak with 4 weeks Can involve cranial nerves Can cause respiratory muscle weakness Autonomic involvement less common	GM1, GM1b, GD1a	No features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LLN Sensory action amplitudes < LLN
Acute sensory neuropathy		GD1b	
Acute pandysautonomia / regional variants	Fisher's syndrome Triad: Acute ophthalmoplegia, Ataxia, Areflexia May have facial and lower cranial nerve involvement Generally benign	GQ1b, GT1a	Sensory nerve demyelination with sensory nerve conduction slowing
	Oropharyngeal	GT1a	
Overlap – Fisher's syndrome / Guillain–Barré syndrome overlap syndrome	Overlap forms of Fisher's syndrome with limb weakness and respiratory involvement not uncommon	GQ1b, GM1, GM1b, GD1a, GalNac-GD1a	

dCMAP, compound muscle action potential amplitude after distal stimulation; LLN, lower limit of normal; pCMAP, compound muscle action potential amplitude after proximal stimulation; ULN, upper limit of normal.

degeneration or dysfunction. Common findings in GBS are signs of conduction block, prolonged distal latencies and delayed F waves. A further common finding in GBS is a normal sural sensory action potential (SAP) and abnormally small median SAP, the 'normal sural–abnormal median pattern'. Raised cerebrospinal fluid protein (higher the longer the evolution of the illness) with a normal white cell count is characteristic but not specific in GBS. Nerve biopsy can differentiate between demyelination and axonal disease but is seldom performed in GBS.

How is GBS treated?

Immunologic therapies

Results of international trials have shown equivalent efficacy of intravenous immunoglobulin (IVIg) and plasma exchange, but not corticosteroids, and these treatments minimise worsening, hasten recovery and reduce long-term disability. IVIg is usually preferred because it is more convenient with fewer side effects, although potential side effects include anaphylactic reactions, dermatitis and

Box 3.63 **Diagnostic criteria in Guillain–Barré syndrome**

Absolute requirements

- Progressive weakness
- Areflexia
- < 4 weeks of illness

Supportive criteria

- Relative symmetry of signs
- Mild sensory symptoms or signs
- Cranial nerve involvement
- Recovery beginning 2–4 weeks after progression ceases
- Autonomic dysfunction

Supportive laboratory features

- Elevated cerebrospinal fluid protein and cell count < 10 µ/l (a count of over this raises the possibility of leptomeningeal malignancy, human immunodeficiency virus or an alternative infectious diagnosis, e.g. Lyme disease or poliomyelitis)
- Electrodiagnostic features of conduction slowing or block

Table 3.59 Investigations in Guillain–Barré syndrome

To establish diagnosis	Electrodiagnostic studies – minimum study comprises three sensory nerves (conduction velocity and amplitude), three motor nerves (conduction velocity, amplitude and distal latency) with F waves and bilateral tibial H reflexes Cerebrospinal fluid examination (raised protein)
To establish cause	Stool culture and serolgy for *Campylobacter jejuni* Stool culture for poliovirus in pure motor syndromes Acute and convalescent serology for cytomegalovius, Epstein–Barr virus and *Mycoplasma pneumoniae* Antibodies to gangliosides GM1, GD1a and GQ1b
General monitoring	Urinalysis Haematobiochemistry Chest radiograph Spirometry
In certain circumstances	Neuroimaging Creatinine kinase Acetylcholine receptor antibodies Antinuclear antibody Urine porphobilinogen and δ-aminolaevulinic acid Drug and toxin screen Human immunodeficiency virus test

hyperviscosity including stroke and venous thromboembolism. The earlier treatment is started, the better the outcome, best in the first 2 weeks and no more than four exchanges are worthwhile since further exchanges produce no further benefit. The standard regimen is 0.4 g/kg daily for 5 days (2 g/kg in total), although the minimum required dose to accelerate recovery is unclear, as is the value of a second course in those who fail to respond initially.

Corticosteroid ineffectiveness is unusual in an inflammatory disease, and in GBS may imply that the immunological damage has already occurred or it may be that steroids interfere with nerve repair. It is unclear how IVIg works, but it is probably multifactorial inclusive of provision of anti-idiotype antibodies, blockade of Fc receptors, interference with complement activation, and catabolism of antibodies. Subacute forms of disease and chronic inflammatory demyelinating polyneuropathy behave differently from GBS and may respond to steroids.

Other potential therapies worthy of more research include biological agents against antigangliosides and against complement, prophylactic antibiotics against *C. jejuni* infection, and physiotherapy.

General therapies

Supportive and essential adjuncts to immunological therapies are less evidence-based but supported by multidisciplinary consensus groups and include:

- High-dependency/intensive care unit initially
- Electrocardiogram (ECG) and cardiac monitoring since autonomic disturbance can produce arrhythmias
- 4-hourly forced vital capacity until improvement (not peak expiratory flow or arterial blood gases since these may not become abnormal until a peri-arrest stage); apparent improvement may occur before decline
- Thromboembolic deterrent (TED) stockings/prophylactic low-molecular-weight heparin
- Nasogastric tube feeding
- Analgesia (carbamazepine, gabapentin, tricyclics, opiates)
- Physiotherapy
- Foot splints and orthotics.

What are the potential outcomes of GBS and can these be predicted?

There is 3.5–12% mortality in the acute phase. At 1 year, approximately two-thirds have recovered and the remainder have varying degrees of disability. Outcomes appear worse in older people, those with severe deficits and peaks, and those with extensive clinical or electrophysiological axonal damage.

What do you know about West Nile virus?

This is a Flaviviridae arbovirus whose *Cutex* spp. mosquito vector is present in the UK and which may increase in prevalence in the next few years. Around 20% of those infected develop West Nile virus, and some will develop neuroinvasive disease producing similar clinical features to poliomyelitis. Older people seem to be more often affected. Features include fever, headache, fatigue, exanthema, myoclonus in 30%, radicular back pains, rapidly ascending weakness, areflexia and sometimes meningoencephalitis. Bladder dysfunction is common and often an important clue. White cell count elevation is modest, and leucopenia and thrombocytopenia occur in some. Hyponatraemia affects 50%, and liver function abnormalities 25%. Cerebrospinal fluid protein levels can be exceptionally high (0.75–1g/l), and glucose is normal. Electromyography shows anterior horn cell dysfunction.

What do you know about wound botulism?

This is increasingly common, especially in intravenous or skin-popping drug abusers. The incubation period is 4–14 days. The botulinum toxin blocks cholinergic neuromuscular junction transmission presynaptically, causing motor weakness. Motor weakness tends to affect bulbar and extraocular muscle function initially and then progresses in a descending fashion. Autonomic symptoms such as dry mouth and blurred vision are very likely. Treatment is supportive. Antitoxin is given, along with antibiotics against *Clostridium*, with wound debridement where needed, although these measures only help halt the 'disease-horse', which has already bolted, in its tracks. It carries a high mortality, often through respiratory depression, and those who recover are in for the 'long-haul', usually many weeks or months of aggressive supportive care and rehabilitation.

What do you know about the periodic paralyses?

Periodic paralyses may be driven by genetic predisposition or other metabolic causes such as thyroid disturbance. Hypokalaemic and hyperkalaemic varieties are not uncommon and characteristically there is periodic acute flaccid paralysis (that if not careful is misdiagnosed as psychologically generated) which can last for days or which produces morning attacks, patients being entirely well with normal biochemistry between attacks. Common precipitants of hypokalaemic periodic paralysis are a high carbohydrate and salt diet (such as pizza and chips), and exercise, and hypokalaemia is then captured, often with ECG abnormalities, and a raised creatinine kinase. Compound muscle action potentials are also abnormal. Provocation testing with glucose and insulin is not recommended but is capable of making the diagnosis.

CASE 3.48 MYASTHENIA GRAVIS

Instruction

Please examine this patient's eye movements/arms and discuss your findings.

Recognition

There is *weakness of the extraocular muscles* giving rise to a *complex ophthalmoplegia* and unilateral or bilateral *ptosis* (the pupil is never involved) and *weakness of proximal limb muscles* (weakness of elbow and finger flexion is not uncommon).

Weakness is induced or worsened by sustained activity – *fatigability*. Ptosis and diplopia are worsened by 2 minutes of upward gaze (Fig. 3.96).

Bulbar muscle weakness may occur, with *dysarthria (nasal speech)* and *dysphagia*. Facial involvement may cause difficulty with eye closure and a snarling smile, and weakness of jaw closure may cause chewing difficulty. Trunk involvement may occur. Neck muscle weakness may cause head drooping.

Interpretation

Confirm the diagnosis

Features that can help differentiate myasthenia from alternative diagnoses are shown in Box 3.64.

What to do next – assess other systems

Look for overt signs of other autoimmune diseases, e.g. Graves' disease (3%).

Consider severity/decompensation/complications

Tell the examiners that:

- Respiratory muscle involvement can be life-threatening; dyspnoea, particularly lying supine, is common owing to diaphragmatic weakness. Forced vital capacity is monitored.
- Aspiration pneumonia is a potential complication with bulbar myasthenia.

Consider function

Tell the examiners that limb weakness, diplopia and bulbar palsy can have devastating effects on physical and psychological health.

Box 3.64 **Features that differentiate myasthenia from alternative diagnoses**

- Fatigable weakness is absolutely characteristic of myasthenia
- Non-limb features of generalised myasthenia (ocular and bulbar dysfunction) are not features of most myopathies
- Muscle wasting may be a feature of neuropathies and myopathies but not myasthenia
- Tendon reflexes are normal or slightly brisk in myasthenia but reduced in peripheral neuropathies
- Chronic progressive external ophthalmoplegia (a mitochondrial disorder) can mimic the ocular symptoms of myasthenia but fatigue is not typical

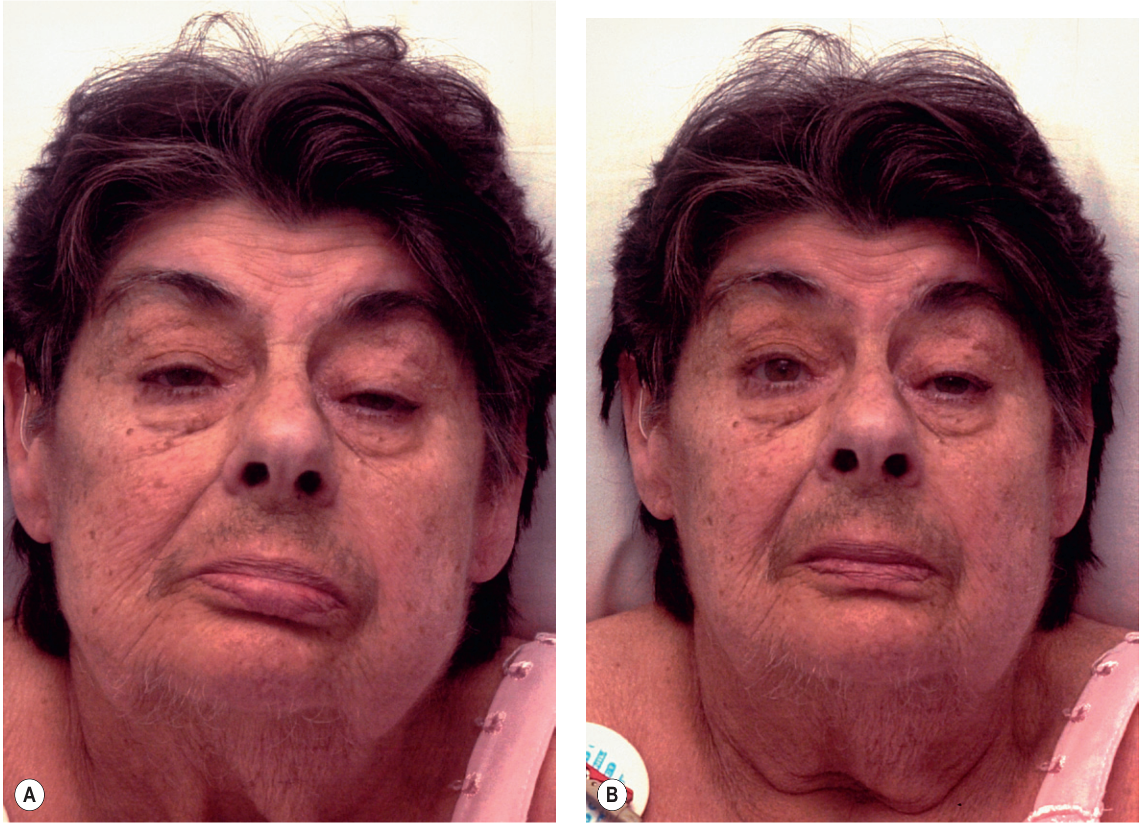


Figure 3.96 Myasthenia gravis: (A) ptosis and facial weakness, (B) some improvement after Tensilon.

Discussion

What causes myasthenia gravis?

It is an autoimmune disease of the neuromuscular junction in which autoantibodies directed against the postsynaptic acetylcholine receptor (AchR) of the neuromuscular junction cause functional blockade and destruction of receptors. About 85% of patients with generalised myasthenia are seropositive and 55% with isolated ocular myasthenia. About 40% of patients with seronegative generalised myasthenia have autoantibodies to the postsynaptic protein muscle-specific kinase (MuSK). Antibody titre does not correlate with disease activity or progression. The thymus is important in pathogenesis, the normal thymus a source of AchR; expression may be upregulated in patients with thymoma. The thymus may also have a role in deleting autoreactive T cells specific for self-antigens, and thus any disturbance of function allowing escape of such cells. The hyperplastic thymus may also be a site of anti-AchR production.

Who tends to be affected?

It affects all races and ages and has a prevalence of around 1/7000 and an incidence of 1/100 000. There are five subtypes with useful treatment implications (Box 3.65).

Box 3.65 **Subtypes of myasthenia gravis**

- Early-onset (age < 40 years) myasthenia with thymic hyperplasia, *HLA B8DR3* association and a 4:1 female–male ratio
- Late-onset myasthenia with thymic atrophy, *HLA B7, DR2* association and a 1:2 female–male ratio (most common subtype)
- Thymoma without HLA association and a 1:1 female–male ratio
- Ocular myasthenia (20% of patients have pure ocular myasthenia)
- A MuSK antibody-positive group that overlaps with late-onset seronegative patients

How useful are AchR antibodies diagnostically?

AchR antibodies are detectable in most patients; a negative test does not exclude but a positive test is highly specific.

What is the role of anticholinesterase testing?

A positive response to anticholinesterases (e.g. oral pyridostigmine) is common, and pyridostigmine is also first-line treatment. The *Tensilon* test with intravenous edrophonium (Tensilon) assesses immediate and short-acting effects of anticholinesterase, but there is a risk of bradycardia and other cholinergic side effects. With antibody testing and electromyography, Tensilon testing is now less common.

Does electromyography (EMG) help diagnostically?

It shows decreasing muscle action potentials with repetitive stimulation. Increased jitter and blocking is found on single-fibre EMG and the diagnosis is questioned when single-fibre studies in weak muscle are normal. Abnormal single-fibre EMG can be found in motor neurone disease and some myopathies.

Should all patients have mediastinal imaging?

This is good practice, to characterise thymic pathology.

How is myasthenia gravis treated?

Treatments are outlined in Box 3.66.

What is the prognosis in myasthenia gravis?

Treatment is usually needed lifelong and mortality slightly increased.

List some causes of a myasthenic crisis

- Tiredness
- Infection
- Drugs (many)

What is Lambert–Eaton myasthenic syndrome (LEMS)?

LEMS is much less common than myasthenia, and more common after the fifth decade. Sixty per cent of cases are associated with small-cell lung cancer, as a paraneoplastic syndrome. LEMS also has an autoimmune basis with antibodies to P/Q-type voltage-gated calcium channels in most patients. Autoantibodies to these channels on malignant cells are thought to cross-react with those at the presynaptic membrane of the neuromuscular junction. LEMS may precede cancer by up to 5 years, and even be associated with tumour suppression. LEMS causes fatigability but does not affect ocular or bulbar muscles, nor cause ptosis. Reflexes are absent but return with exercise, unlike myasthenia gravis, and the EMG shows improved amplitude with repetitive stimulation. LEMS can be treated with 3,4-diaminopyridine in specialist centres. Anticholinesterases tend to be less effective.

Box 3.66 **Treatments for myasthenia gravis**

Anticholinesterase

First-line treatment is usually pyridostigmine, a long-acting cholinesterase inhibitor, slowly titrated up to 60 mg three or four times daily. Cholinergic side effects include abdominal cramps and diarrhoea and can be controlled with anticholinergic drugs such as propantheline bromide 15 mg thrice daily. High doses of anticholinesterase can precipitate a cholinergic crisis causing worsening weakness or pulmonary oedema. A need for more than 90 mg of four times daily indicates a need for immunosuppression.

Immunosuppression

Prednisolone alone, or with azathioprine as a steroid-sparing agent, is first-line immunosuppression. Treatment should be started in hospital in all but the mildest cases since steroids can initially exacerbate symptoms and impair ventilatory capacity. Slowly introducing prednisolone reduces the risk with a target of 1.5 mg/kg. Azathioprine should be prescribed only after exclusion of low thiopurine methyltransferase activity, which would cause slow metabolism of azathioprine and is a contraindication. There is no evidence for teratogenicity of prednisolone or azathioprine. Other immunosuppressants are seldom used.

Remission

Anticholinesterase should be withdrawn, and, if still free of symptoms, prednisolone is withdrawn slowly to the lowest dose that maintains remission.

Ocular myasthenia

This is relatively benign, with seldom a need for more than anticholinesterases and low-dose steroid.

Surgery

The benefits of thymectomy are not conclusively established, but it is generally recommended in those in whom onset occurs under 40 years of age, and generally soon after diagnosis.

Non-response

Misdiagnosis and rare, congenital myasthenic syndromes are reasons for a failed response to immunotherapies.

CASE 3.49 MYOPATHY AND MYOSITIS

Instruction

Please examine this patient's arms and legs and discuss your findings.

Recognition

There is *symmetrical weakness* (and possibly wasting) in the *proximal muscles* (Fig. 3.97). There is *inability to rise from a squatting position or to raise the arms above the head*. There are no other neurological signs.

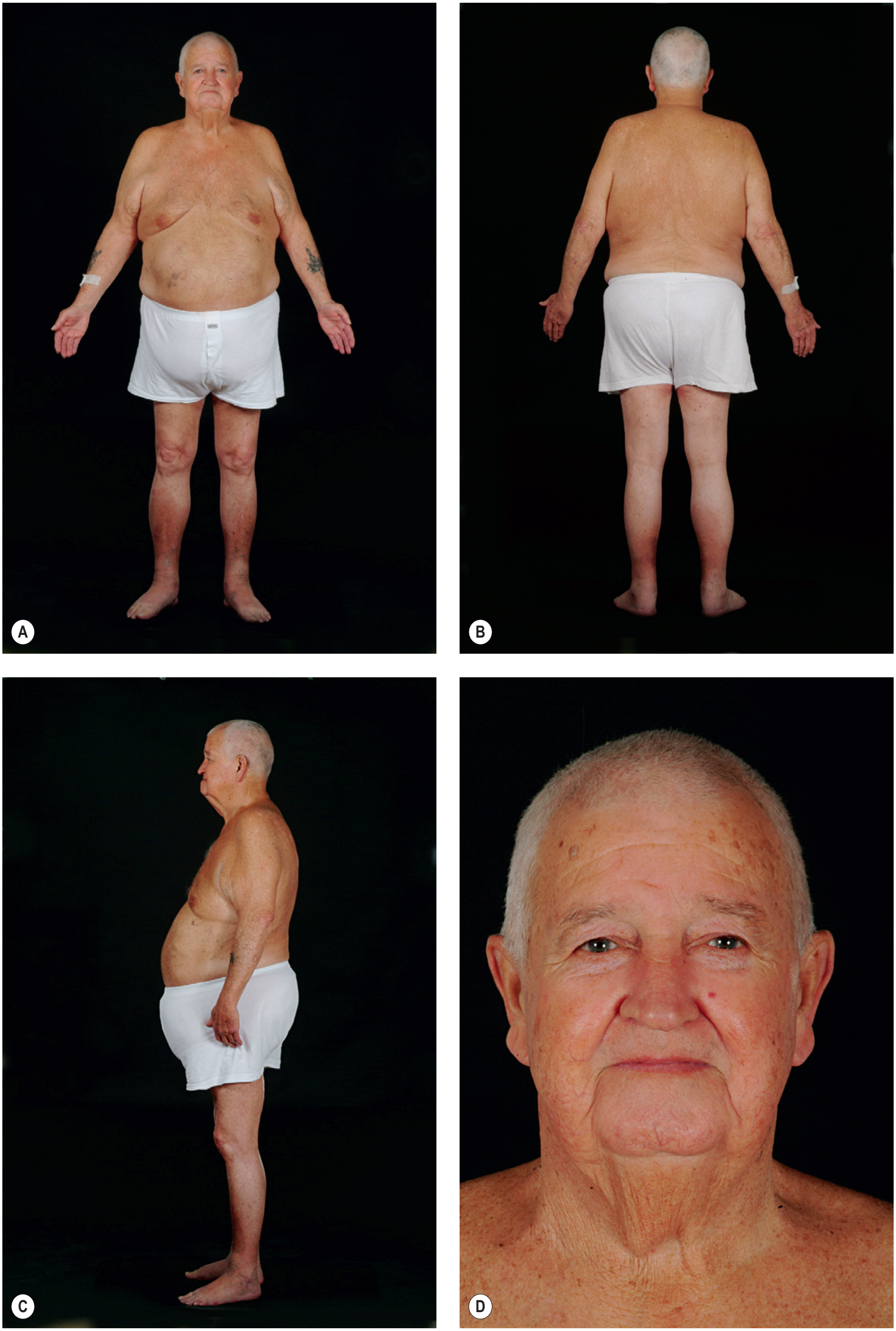


Figure 3.97 (A–D) Cushing's syndrome.

Interpretation

Confirm the diagnosis

Features that can help differentiate myopathy from myasthenia or neuropathy are shown in Box 3.67. Tell the examiners that the diagnosis of the type of myopathy may be based on history and clinical features, and biopsy (Fig. 3.98).

What to do next – consider causes

The more common of many potential causes with potential diagnostic clues are listed in Table 3.60.

Consider severity / decompensation / complications

This depends on the underlying cause (Table 3.60).

Consider function

Tell the examiners that life would be very restricted, obvious problems being lifting objects overhead, combing and washing hair, climbing stairs and rising from a chair.

Discussion

What is myositis and what types of myositis are there?

Myositis is inflammation of skeletal muscle and has many causes (Box 3.68).

Box 3.67 Features that differentiate myopathy from myasthenia or neuropathy

- Proximal muscle weakness is usually due to myopathy
- Distal muscle weakness is sometimes due to myopathy, but much more commonly due to peripheral neuropathy
- Myasthenia gravis is unusual without ophthalmoplegia or ptosis or bulbar symptoms, and characteristically fatigable

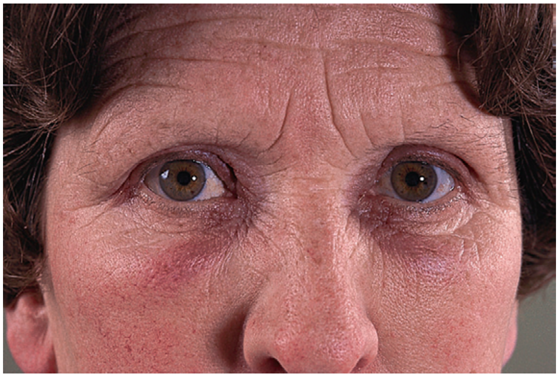


Figure 3.98 Dermatomyositis.

What are the similarities and differences between the common types of myositis?

These are outlined in Table 3.61.

How would you screen for malignancy in polymyositis / dermatomyositis?

There is no absolute consensus as to what is appropriate. Chest X-ray, abdominal and pelvic ultrasound, breast examination and mammography, and ovarian tumour markers or prostate specific antigen are performed by many physicians, with possibly a computed tomography scan of the chest in smokers. A barium swallow and endoscopy are needed for dysphagia.

Does magnetic resonance imaging have a place in investigating myositis?

It can help localise inflammation and target biopsy.

Does biopsy usually further the diagnosis in myositis?

Biopsy is very helpful but should be from a likely site such as deltoid or quadriceps and very weak muscle should be avoided since burnt out fibrosis may be all that is seen. Prior arrangement with a pathologist is essential since specimens should be handled immediately, fresh specimens for biochemistry and frozen specimens for light and electron microscopy.

Does electromyography further the diagnosis in myositis?

Spontaneous muscle fibrillation, complex repetitive discharges, positive sharp waves at rest and short duration,

Box 3.68 Causes of myositis

Idiopathic myositis

- Primary idiopathic polymyositis
- Primary idiopathic dermatomyositis
- Polymyositis / dermatomyositis associated with neoplasia
- Polymyositis / dermatomyositis associated with autoimmune disease
- Inclusion body myositis

Infection

- Viral, e.g. influenza, hepatitis B, coxsackievirus, echovirus, human immunodeficiency virus
- Bacterial, e.g. *Staphylococcus*, *Streptococcus*, *Clostridium*, *Mycobacterium*
- Parasitic, e.g. toxoplasmosis

Drugs

- Cholesterol-lowering agents, e.g. statins, fibrates
- Antibiotics, e.g. rifampicin, sulfonamides, zidovudine
- Other, e.g. angiotensin-converting enzyme inhibitors, colchicines, penicillamine

Table 3.60 Causes of myopathy and potential clues

	Causes		**Diagnostic clues**
Acquired myopathies	Inflammatory myopathies (myositis)	Polymyositis	May be painful and tender
		Dermatomyositis	Rash
		Inclusion body myositis	Marked distal atrophy
		Other, e.g. drugs	History
	Metabolic/endocrine myopathies	Cushing's syndrome	Cushingoid morphology
		Thyrotoxicosis or hypothyroidism	Hypothyroid face
		Acromegaly	Acromegalic morphology
		Hypoadrenalism	Hyperpigmentation if Addison's disease
		Osteomalacia	Common in older people
		Carcinoma/paraneoplastic neuromyopathy	Weight loss
		Alcohol	History
		Hypophosphataemia	Phosphate level
Genetic myopathies	Muscular dystrophies	Muscular dystrophies with predominant axial or limb-girdle weakness	See text
		Non-limb-girdle muscular dystrophies with cranial muscles involvement	
		Distal myopathies	
	Congenital myopathies	Many, e.g. centronuclear myopathy Tend to be non-progressive	Distal weakness Long, thin face High-arched palate
	Muscle ion channel disorders	Myotonic dystrophy (DM1)	Myotonia (impaired muscle relaxation) Distal weakness
		Proximal myotonic myopathy (PROMM or DM2)	Proximal weakness
		Non-dystrophic myotonias and periodic paralyses	Myotonia and/or periodic paralysis
	Genetically determined metabolic myopathies	McArdle's disease and storage diseases	Myalgia on exercise
		Mitochondrial disorders	Isolated or with central nervous system symptoms
		Rarities, e.g. malignant hyperthermia	

decreased amplitude discharges on contraction are all common, non-specific features.

What do you know about the muscular dystrophies?

This is a group of disorders characterised by fibre necrosis and replacement of muscle by fat and fibrous tissue.

Muscular dystrophies with predominant axial or limb-girdle weakness

■ **Duchenne muscular dystrophy.** This is X linked, the gene responsible on the short arm of the X chromosome. A translocation at the locus, Xp21, prevents production of a protein called dystrophin. Patients develop severe proximal myopathy and pseudohypertrophy of the calf muscles in early childhood with difficulty in rising to standing position – the hands 'walk up' the front of the legs to assist standing (Gower's sign). In childhood the gait is waddling but patients are invariably wheelchair bound before their teens. Death is common in the second or third decades due to respiratory infection. Tall R waves may be present on the electrocardiogram and cardiac failure is not unusual. Becker's muscular dystrophy is a milder form, with dystrophin produced in smaller quantities than normal. In neither is facial weakness predominant.

■ **Limb girdle muscular dystrophies.** These are the commonest muscular dystrophies in adults, presenting in the second or third decade, and are a heterogeneous group involving the upper and the lower limbs, generally starting proximally. Neck muscles may become weak but facial and bulbar muscles are not affected. The group is

Table 3.61 Common types of myositis

		Polymyositis	Dermatomyositis	Inclusion body myositis
Age of onset		Older age group > 50 years	Younger adults Children	The most common inflammatory myopathy > 50 years
Cause		Unknown		Unknown
Pathology		Autoimmune to muscle antigen Th1 pro-inflammatory disease IFN-γ, IL-2 and TNF-α provoke interstitial, intracellular muscle damage	Immune mediated by complement Perivascular damage	Minimal inflammation Inclusion bodies within vacuoles or within cells (though vacuoles may be empty), commonly staining for β-amyloid
Muscle symptoms	Onset	Insidious and subacute over weeks to months		Slowly progressive Often present for years before diagnosis
	Weakness (the most common symptom)	Symmetrical Proximal (distal rare)		Asymmetry common Proximal and distal Finger flexion weakness and foot drop are common
	Atrophy	Uncommon		Marked, especially distally, similar to amyotrophic lateral sclerosis
	Myalgia	Painful in about 50%		Painless
	Facial / bulbar involvement	Rare, e.g. dysphagia, hoarseness, dysphonia		Does not occur
	Ocular involvement	Never		
Extra-muscular involvement	Skin	No	With or without myositis Heliotrope rash – violaceous eyelids, malar area, 'V' area of anterior chest and upper back Gottron's papules – purple-red, scaly plaques on knuckles and fingers often extending to forearms	No
	Calcinosis	Occasional, intracutaneous, subcutaneous, fascial and intramuscular		No
	Joints	Common Symmetrical large joints		No
	Gastrointestinal	Dysphagia		No
	Lung	Diffuse parenchymal lung disease Aspiration		No
	Cardiovascular	Raynaud's phenomenon Myocarditis Pericarditis		No
	Renal	Proteinuria Nephrotic syndrome Mesangial proliferative glomerulonephritis		No
	Constitutional symptoms	Fatigue Fever Anorexia Weight loss		Less likely
Complications	Malignancy	Risk increased, especially dermatomyositis / men over 45 years Estimated 5% prevalence		No increased risk

Table 3.61 Common types of myositis—cont'd

		Polymyositis	**Dermatomyositis**	**Inclusion body myositis**
Investigations	Creatine kinase	5–50× normal Other muscle enzymes, e.g. transaminases, LDH may be raised		Normal since limited inflammation
	ESR/C-reactive protein	Usually moderately elevated		
	ANA	> 80% positive ENAs include Ro (SS-A), U1 (ribonucleoprotein, centromere, mitochondria) and tRNA synthase. Other myositis-specific autoantibodies include anti-signal recognition particle (anti-SRP), anti-M2 and anti-PM-Scl (a subset with systemic sclerosis)		Positive in small minority
Treatment		Good response to steroids (high dose initially, e.g. 60 mg prednisolone) Steroid-sparing agents, e.g. azathioprine, methotrexate, ciclosporin	Intravenous immunoglobulin effective in steroid-resistant dermatomyositis	No effective treatment
		At this stage a specialist (rheumatologist, neurologist or immunologist) should be involved		
Monitoring		Muscle power Creatine kinase For treatment complications, e.g. bone densitometry		
Prognosis		80% 5-year survival About one-third die of disease, one-third remain weak and one-third return to normal		Inevitable progression

ANA, antinuclear antibody; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; Th, T helper; TNF, tumour necrosis factor.

inherited in an autosomal recessive fashion. Life expectancy is normal.

Non-limb-girdle muscular dystrophies with cranial muscle involvement

■ **Fascioscapulohumeral muscular dystrophy.** This affects the face and shoulder girdle. There is marked facial weakness with impaired expression and difficulty smiling, whistling and closing the eyes. The lips at rest are slack, the mouth open. There is dysarthria due to weakness of the buccal muscles. The neck muscles are weak, as are the shoulder girdle muscles with winging of the scapula. Onset is often in early adult life with a normal life expectancy. It is autosomal dominant.

■ **Oculopharyngeal muscular dystrophy.** This presents with ptosis and weakness of extraocular muscles and bulbar muscles.

Why do glycogen storage diseases cause myalgia?

In McArdle's disease, the commonest storage disorder, deficient myophosphorylase results in failure to break down glycogen to glucose. Severe myalgia develops soon after the start of exercise with cramp (electrically silent muscle contracture) until alternative energy sources are mobilised.

What are mitochondrial cytopathies?

These can affect muscle specifically or as part of a multisystem disorder, typically involving the central nervous system. Large deletions or point mutations in mitochondrial DNA cause Kearns–Sayre syndrome, a chronic, progressive external ophthalmoplegia, MELAS (mitochondrial encephalopathy, lactic acidosis and strokes) and MERRF (myoclonus, epilepsy and ragged red fibres).

How is polymyalgia usually distinguished from myositis or other myopathies?

Polymyalgia typically causes stiffness and weakness, and is less tender than myositis. Muscle enzymes are normal, but the erythrocyte sedimentation rate is generally higher than that of myositis.

CASE 3.50 MYOTONIC DYSTROPHY

Instruction

Please examine this patient's muscle strength and proceed as you think best.

Recognition

The *face is myopathic* (it looks sad, sleepy and lifeless) with *bilateral ptosis*. There is *wasting of temporalis muscles* causing hollowing of the temples, and there may be wasting of other facial muscles, neck muscles and muscles of the shoulder girdle. There is *distal weakness and wasting*. There is *frontalis muscle wasting* and the *forehead is smooth*, with *frontal balding* (Figs 3.99–3.102).

When you shake hands you may notice *slow release of grip*. The same occurs if the patient is asked to make a fist, and is worse if the patient is cold or excited. *Percussion myotonia* is present on the thenar eminences – when you percuss, a dimple appears which is slow to resolve. There is also slow eyelid opening after firm closure. Tendon reflexes may be attenuated.

Speech is *dysarthic* and *nasal*.

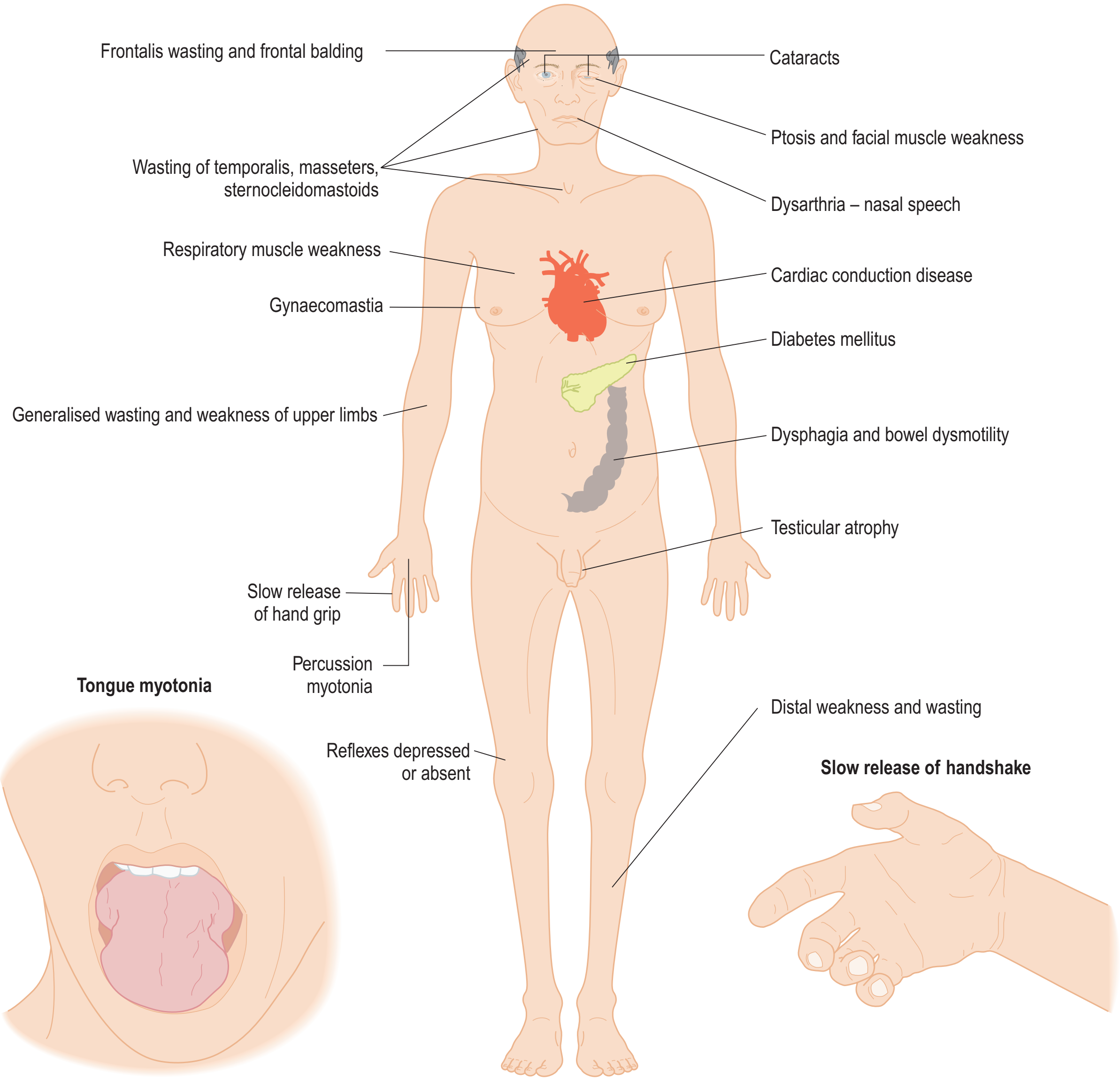

Frontalis wasting and frontal balding
Cataracts
Ptosis and facial muscle weakness
Wasting of temporalis, masseters, sternocleidomastoids
Dysarthria – nasal speech
Respiratory muscle weakness
Cardiac conduction disease
Gynaecomastia
Diabetes mellitus
Generalised wasting and weakness of upper limbs
Dysphagia and bowel dysmotility
Testicular atrophy
Slow release of hand grip
Percussion myotonia
Tongue myotonia
Distal weakness and wasting
Reflexes depressed or absent
Slow release of handshake

Figure 3.99 Myotonic dystrophy.

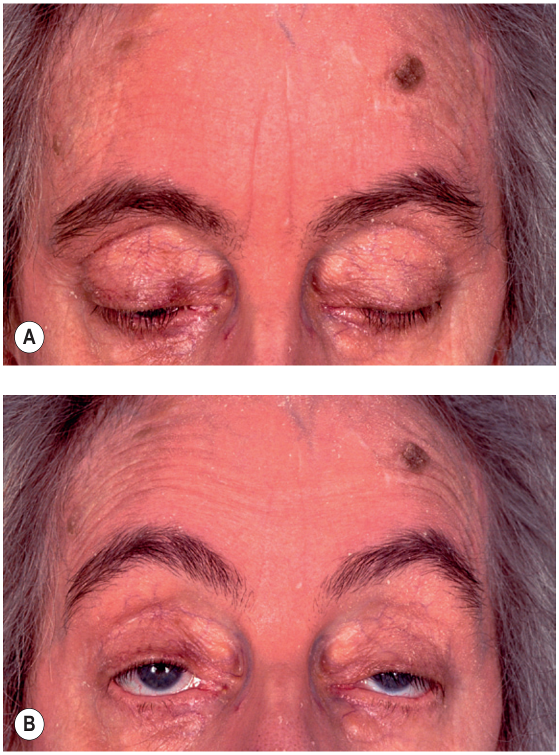


Figure 3.100 Myotonic dystrophy: (A) eyes closed, (B) eyes open with bilateral ptosis.

Interpretation

Confirm the diagnosis

Unlike muscular dystrophies, myotonic dystrophy is a multisystem disorder with an assortment of presentations. Classic myotonic dystrophy patients have myotonia, weakness and a range of other features by early to mid-adult life; mild myotonic dystrophy can present in later adult life with subtle myotonia and weakness, or other features such as cataracts or diabetes.

What to do next – assess other systems

Look for cataracts or evidence of cataract surgery, and blepharitis, and then tell the examiners that you would:

- Check for gynaecomastia and testicular atrophy
- Also expect percussion myotonia of the tongue
- Ask about gastrointestinal symptoms, which include dysphagia, delayed gastric emptying, bowel dysmotility and small bowel bacterial overgrowth.

Consider severity / decompensation / complications

Tell the examiners that:

- Disease progresses very slowly; grip myotonia is often the first symptom, muscle weakness and wasting then starting distally and at the sternocleidomastoids with proximal involvement a late sign
- Diabetes mellitus is increased four-fold
- Cardiac conduction abnormalities are common; cardiomyopathy can occur but is less common
- Respiratory complications account for 30–40% of deaths
- Patients are at increased risk from general anaesthesia.

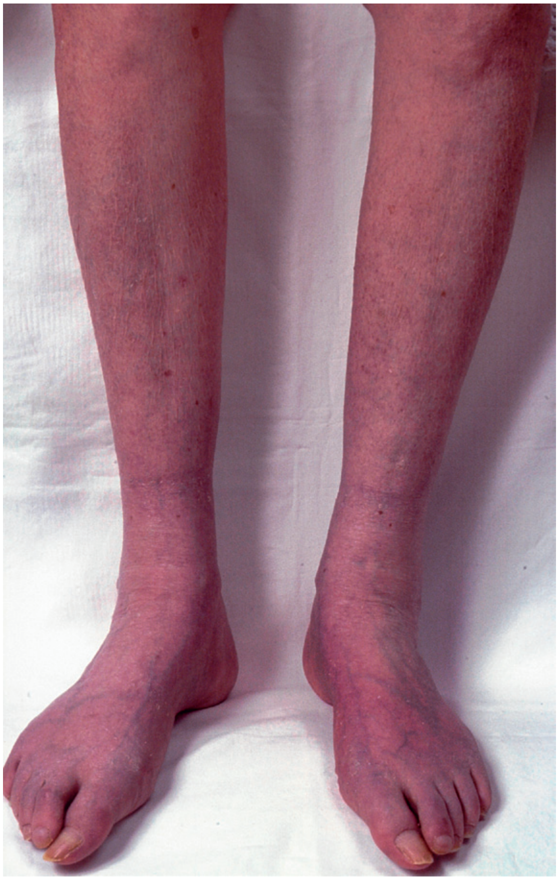


Figure 3.101 Myotonic dystrophy – distal wasting of lower limbs.

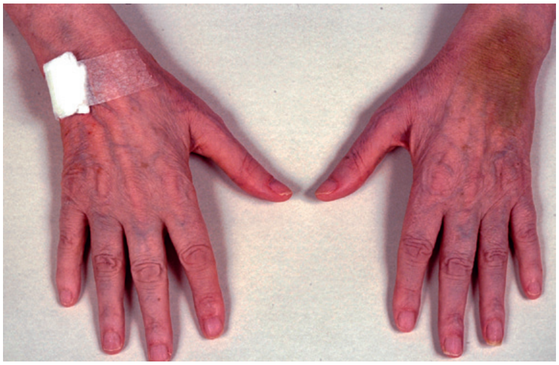


Figure 3.102 Myotonic dystrophy – diffuse wasting of hand muscles.

Consider function

The non-neuromuscular symptoms described above can be disabling. Hypersomnolence is also very common, and does not correlate with the severity of muscle involvement.

Discussion

What do you understand by the term myotonia?

Myotonia implies continued contraction of muscles after voluntary contraction with slow, delayed relaxation.

What is the genetic basis of myotonic dystrophy?

Myotonic dystrophy type 1 (other types are rare) is a progressive, inherited muscular dystrophy with a prevalence of about 1 in 8000. It is an autosomal dominant condition on chromosome 19, with an equal male–female ratio, and one of numerous neurogenetic disorders caused by expansion in the size of a three-base-pair (triplet or trinucleotide) repeat sequence. In myotonic dystrophy the triplet repeat is CTG, occurring up to 35 times in unaffected individuals but more than 50 times in myotonic dystrophy; generally, 50–100 repeats is mild, 200–500 repeats results in classic myotonic dystrophy and those more than 1000 repeats have congenital or childhood onset disease. Triplet expansion increases with successive generations, a phenomenon known as genetic anticipation.

How does the triplet repeat cause disease?

The CTG repeat mutation on the *DMPK* gene is outside the sequence of mRNA that is translated into protein, but many effects are due to the abnormal, expanded mRNA binding to nuclear proteins that in turn affect processing of other genes. Changes affecting insulin receptor mRNA and muscle chloride mRNA cause insulin resistance and myotonia, respectively. Reduced DMPK protein as a result of the mutation affects ion channels, altering skeletal and cardiac muscle excitability. The mutation affects the amount of protein made by adjacent genes, and reduced levels in one of these, SIX5, is implicated in cataract development.

Are mildly affected adults easy to miss?

Mild weakness of grip or myotonia in late adulthood is often overlooked by the patient.

Do mildly affected adults have an increased cardiac risk?

Cardiac complications still occur and surveillance is required.

What is myotonia congenita?

This refers to delayed relaxation after muscle contraction, without other features of myotonic dystrophy.

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Communication skills and ethics

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Introduction to communication skills and ethics

COMMUNICATION SKILLS

Effective communication

Effective communication in medicine means simply that doctor and patient (relative, colleague, etc.) understand each other. We could, broadly, consider two stages to an encounter with a patient. The first stage is concerned with information gathering. The aim is to answer the question: 'What is the problem or what are the problems?' The second stage is concerned with developing a management plan, aiming to answer the question: 'How do I solve this problem or these problems?' Management plans should be developed not just for patients, but also with patients. A plan is seldom a case of saying:

> You have an overactive thyroid; you will need to take a tablet called carbimazole,

but more a case of:

> Let's look at how we could treat your overactive thyroid.

It is a two-way process of information sharing. The doctor does not so much know the solution to the problem (although may know what is clinically best), but reach a solution through communicating with the patient. This method of problem solving is more patient centred.

Doctor- and patient-centred communication

At first sight, allowing patients to be involved in management decisions might seem to be relinquishing medical expertise and merely facilitating what patients want. This would be unprofessional, and we could deservedly question how patients can know what they want without medical knowledge and training. Were you to say to the thyrotoxic patient:

> We could treat your overactive thyroid with tablets called carbimazole or we could use radiotherapy or we could arrange for you to have an operation. Now which will it be?

she would probably respond:

> Well, I don't know what's best. You're the doctor.

Patient-centred communication does not mean abdicating decision making to patients. It is the process of providing patients with the appropriate knowledge and understanding to enable them to make informed decisions and take appropriate responsibility for their care. Such an approach combines the professional knowledge and opinions of the doctor with respect for the autonomy of the patient. A better way to approach the thyrotoxic patient would be:

> There are a number of ways to treat an overactive thyroid. One would be to take tablets for a few months to see if they settle it down. They are often very effective, although some patients do eventually need to have an operation. Another choice would be to consider surgery at the outset, but in my experience most surgeons prefer to operate if tablets don't work. A third option would be something called radiotherapy, but this may not be a good idea if you were planning to become pregnant in the near future. I usually prefer patients to take advice from a doctor who specialises in thyroid problems before deciding, but wonder if you have any immediate thoughts about these treatments.

The degree to which we engage in open discussion depends upon the patient. At one end of the spectrum are patients with seemingly very little interest in decision participation – *I'll go with whatever you think is best, doctor*. At the other extreme are patients who ruminate over everything that happens to them, and want to know everything – *How many stitches would the surgeon need to use, doctor?*

Patients differ. Yet when we look for evidence-based management of disease, we find management plans that focus on disease and not the permutations of our patients.

Traditionally, doctors have been *disease centred*, but diseases are wrapped in packages that are patients and a fundamental clinical skill is applying evidence-based medicine to the spectrum of different patients. Guidelines might advise against radioactive iodine in pregnancy and the patient might say:

> I was thinking about having a family soon.

But she might also say:

> My mother had a thyroidectomy 30 years ago and had terrible swallowing problems afterwards until the day she died.

Those swallowing problems may not have been associated with the thyroidectomy. One could also say that surgery has moved forward in 30 years. But the patient may nevertheless have decided she does not want to contemplate surgery. The point is that the *optimal management of a disease is not automatically the optimal management for a patient with that disease*.

Taking into account how a patient feels about their disease and its management is what is meant by *patient centredness*. Pure *doctor centredness* is doctor controlled and tends to be inflexible from patient to patient. Management decisions are made by the doctor and the patient is expected to comply. The key to patient centredness is not to abandon the strengths of disease and doctor-centred practice, but to share information so that decisions about management are shared with and acceptable to the patient. Patient centredness and doctor centredness should work together, the former relating to clinical knowledge of disease and how it should be managed, the latter a means of harnessing the patient's perspective to convert that knowledge into an acceptable management plan. Because patients have a fundamental ethical right to be involved in decisions about managing their disease, doctors have a duty to be patient centred.

Patient centredness is central to helping patients decide what is best for them. Consider that the surgeon of the thyrotoxic patient felt thyroidectomy to be the best course of action. It would certainly be right to explore her understandable concerns about the operation. Negotiating the best course of action for her should address these concerns. A balanced explanation by the surgeon may emphasise the low incidence of serious complications, despite her fears, and include an expectation of what may happen if she does not proceed to surgery now. Despite this process of shared understanding, if the patient, competent to decide and aware of the risks, declines surgery, she is exercising her autonomy. More likely, she will be reassured and begin to find surgery an acceptable option.

Patients have a right to be involved in decisions that affect them. Practising modern medicine is not just about knowledge, but also about the skills to share that knowledge in ways that encourage patients to make sound informed choices. Patients, in general, value our ability to guide. When they are guided, rather than pushed, they are far more likely to keep going along the treatment path we suggest.

ETHICS

The importance of ethical decision making

Every day in medicine we make ethical decisions. Some of these decisions are based on documented professional or legal frameworks. Most are less clearly defined. How much information about the side effects of a drug should we tell a patient, for example?

Ethical decision making involves the application of ethical principles. Often, the decisions we reach seem intuitively right. But intuition, whilst valuable, may alone be inadequate and even detrimental to a patient's care. For one thing, a purely intuitive approach alone may lead to inconsistent behaviour in the way we care for patients, especially those with complex issues. If we aspire to provide the best care, we need to be more analytical.

Ethical principles

Four broad ethical principles underlie ethical decision making (Box 4.1).

Applying ethical principles

Specific cases have a vital role in ethical argument. Ethics is not a science where we agree upon a set of principles and then deduce what is right or wrong from these. Rather, the *implications* of the principles in specific cases must be explored.

Ethical reasoning is an interactive process that involves consideration of individual situations and application of ethical principles. One logical requirement to this process is consistency. If what you believe to be right in one situation seems inconsistent with what you believe to be right in another, you must either identify a morally relevant difference between the two situations or change your view. When considering individual patients and applying ethical principles, foremost in our minds in decision making should be what is deemed in the patient's best interests. It helps, when making a decision, to ask why you have made it and to be able to justify it.

A word on dignity

In recent years the notion of dignity, while emerging primarily from palliative care, has been more formally applied across the spectrum of medicine. The core values of kindness, respect and dignity are indispensable and invariably, although not automatically, allow ethical practice to flourish. Awareness of the A, B, C, D of dignity in health care is of value to some: attitudes (largely about appreciating the patient's situation and your own impact on it), behaviours (professional and respectful disposition and clinical examination, and facilitation of communication), compassion and dialogue. The Royal College of Physicians rightly emphasises the importance of dignity in both clinical practice and professional examinations.

Box 4.1 **Ethical principles**

1. Respect for persons

We have a duty to respect the rights, autonomy and dignity of the person. This duty incorporates concepts such as honesty, truthfulness, sincerity and trust. In medicine, respecting a patient's autonomy is a fundamental ethical principle.

Autonomy is the capacity to think and decide, and act on the basis of such thought and decision, freely and independently. This requires health professionals to provide the necessary information to help patients reach decisions for themselves and respect such decisions even if these do not appear to be the best course of action.

2. Justice

Justice refers to our duty of universal fairness or equity. It incorporates our duty to avoid discrimination, abuse or exploitation of people.

3. Beneficence

The duty to do good (in the medical context, to our patients) is a fundamental guiding ethical principle. It entails doing what is best for patients, but raises the question as to who is the judge of what is best.

Beneficence is often seen as being applied in practice when a health professional determines, by objective assessment, what is in a patient's best interests. The patient's views are encapsulated in the principle of autonomy. Usually, that which the health professional determines and the patient's views lead to the same conclusion, because most patients choose what is objectively in their best interests.

In a sense, beneficence is the first duty of a doctor – to alleviate symptoms and suffering, usually, but not always, through diagnosis and treatment.

4. Non-maleficence

The duty to avoid doing harm runs, in most situations, parallel to the duty to do good. Most treatments carry some risk of doing more harm than good but it does not follow that such treatments should be avoided on the grounds that avoiding harm takes priority over doing good. This said, the first rule of medicine traditionally is, and firmly remains, do no harm.

Cases

Discussing clinical management

CASE 4.1 EXPLAINING A DIAGNOSIS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

Re: Mrs Elizabeth Wright, aged 45 years

Mrs Wright has systemic lupus erythematosus (SLE). She has had a malar rash and pain in her hands for 12 months. Her clinical presentation, together with results of extensive investigations including autoimmune serology and radiology, supports the diagnosis of SLE confined to skin and joints without other multi-systemic involvement. She is here today for results. She is a hospital secretary and very concerned she may need to stop working.

Your task is to explain the diagnosis, addressing her concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Elizabeth Wright is a 45-year-old hospital secretary with two sons. For the last year she has had intermittent but slowly worsening pain in the joints of her hands and a facial rash that is sensitive to sunlight. She is previously very well, takes no medications and is a non-smoker. She has been investigated recently in the outpatient clinic and informed that systemic lupus erythematosus (SLE) is a possibility. She is here today for the results of tests. She is very concerned that she may need to stop working, which she can ill afford as a single mother. She is also concerned because she is aware of a patient in her workplace needing dialysis, and an internet search advised that SLE was not a curable disease and could cause kidney failure. Otherwise she knows very little about SLE.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. *Clarify the task*

Be clear in your own mind what problem or diagnosis needs to be discussed.

> The tests confirm that SLE has very likely been the cause of your problems.

3. *Establish previous experience*

Stronger candidates are guided by patients when giving explanations. They operate within a patient-centred framework. Weaker candidates think 'Oh no! What do I know about SLE?' and proceed to tell their patients very little or far too much, often in a disorganised fashion. Try to establish what your patient knows about their diagnosis before launching into your explanation. Rather than saying:

> SLE is a condition which …

a better approach would be one of:

> Have you heard of this condition before?
>
> I wonder if you know anything about this condition before we start?
>
> Have you any ideas about this condition?
>
> What have you been told so far about this condition?

A specific, uncommon condition like SLE may mean very little to a patient. Other diagnoses such as multiple sclerosis, cancer and rheumatoid arthritis are well known but often poorly understood. Establishing prior knowledge or preconceptions helps determine at what level to start your explanation. She might not know that SLE can be a multisystem disease affecting more than skin and joints. Alternatively, she might say:

> I was reading that it can affect the kidneys and that some patients end up on dialysis. Is that likely to happen to me?

4. *Be alert to ideas, concerns and expectations*

Establishing prior experience can help you understand any specific fears that may relate to it. Throughout your explanation, try to take account of any ideas, concerns and expectations you elicit. Examples of concerns that a patient with SLE might have include no longer being able to go out in the sun, an unsightly rash, arthritis, needing to take drugs or serious complications such as renal failure. Effects of a diagnosis on work, finances and home life are often central concerns.

5. *Frame the explanation*

Try to provide a framework or order to your explanation. You might talk about why SLE occurs ('misdirected' immune system), possible clinical problems and the likely natural history, with and without treatment.

6. *Keep it clear*

Keep your explanation as clear as possible. Use language she will understand (without being patronising), avoiding complex medical terminology. Sometimes it helps to use similar phrases to the patient:

> How does it look on the whole, doctor?
>
> It looks all right, on the whole. Most patients with your condition live a very normal life.

7. *Repeat important information*

This can be an effective way of emphasising 'take home' messages':

> I should emphasise again that most people do not end up with kidney problems or need dialysis. Most patients have skin and joint problems similar to yourself, and these tend to get better with treatment.

8. *Confirm understanding*

It can sometimes be useful to ask the patient to recount what they feel to be the important points of the discussion.

9. *Encourage feedback and invite questions*

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

Be honest in your explanations and prepared to admit uncertainty (with assurance you will seek the answer) if she asks something you cannot answer.

10. *Agree a way forward*

Ensure that there are arrangements for treatment and follow up.

Discussion

Would you tell her that her condition is incurable, if she asked?

The approach to explaining any diagnosis depends upon the diagnosis itself and should be tailored to the patient. Many conditions are potentially serious but treatable, and in this case potentially 'incurable' in that it may return without treatment but nonetheless it is likely to be fully treatable. Other conditions are more palpably 'incurable' such as disseminated malignancy. But few if any conditions are untreatable as palliation is always possible. Words such as incurable are unhelpful, and it is more helpful to tell her that her condition can usually be fully suppressed with treatment.

CASE 4.2 EXPLAINING AN INVESTIGATION

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Roger Thornhill, aged 74 years

Mr Thornhill has been losing weight for 5 months, and feeling slightly breathless on exertion. He has hitherto been a well man, playing golf every day until admission to hospital last week with cough and possible pneumonia. He feels the antibiotics have helped. However, his chest X-ray showed mediastinal widening and a computed tomography (CT) scan confirmed a mass arising from the left hilum, which is likely to be primary lung cancer but possibly lymphoma. He was aware that the chest X-ray showed an abnormal shadow but does not know the results of his CT scan. He has not smoked for 20 years.

Your tasks are to explain the results of the CT scan and discuss bronchoscopy as the best next step.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Roger Thornhill is a 74-year-old man admitted to hospital last week with cough and pneumonia. He has been losing weight for 5 months. Although he feels a little better after antibiotics, he has been told that his chest X-ray shows an abnormal shadow that may not be purely attributable to infection. A chest CT scan has been performed and he is awaiting the results. He has been worried that the scan might show something sinister, like cancer. He has been an active man, playing golf daily. He was widowed 6 years ago. He gave up smoking 20 years ago.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Clarify the task

Be clear in your own mind what investigation needs to be discussed, and the purpose for which it is being performed.

3. Establish previous experience

Try to establish what he knows about the problem before explaining the investigation. Rather than saying:

> You need to have a test called a bronchoscopy,

a better approach might be:

> The chest specialist feels that we should look more closely into this problem of coughing up blood. He suggests some further tests. May I ask you what you've been told about the results of your tests so far?
>
> I know the X-ray wasn't completely normal. What tests does he suggest?
>
> He suggests a test called a bronchoscopy. Have you heard of a bronchoscopy before?

4. Be alert to ideas, concerns and expectations

Establishing prior experience can help you understand any specific fears relating to the potential diagnosis or to the test itself. These should be addressed before proceeding:

> What do you think the X-ray means, doctor? The other doctor said it could be a growth in the lung. I've smoked all my life so I wouldn't be surprised, to be honest with you. Is it bad?
>
> The X-ray does suggest the possibility of a growth in the lung. A bronchoscopy is the best way of knowing this for certain. It's very hard to say what it means for you until we know for sure what it is. Once we know, we are in a much better position to know the best way forward.

5. Frame the explanation

Try to provide a framework for your explanation of the investigation (Box 4.2).

> The bronchoscopy involves passing a flexible telescope with a light on the end into the airways, usually under sedation. If there is anything seen, such as a growth, then the specialist would take a biopsy, a small piece of tissue, from it for closer examination. It is a very common test these days, and generally very safe.

6. Keep it clear

Keep your explanation as clear as possible. Use language he will understand.

7. Repeat important information

This can be an effective way of emphasising 'take home messages'

8. Confirm understanding

It can sometimes be useful to ask the patient to recount what they feel to be the important points of the discussion.

Box 4.2 **Explaining an investigation**

- The purpose of the investigation (usually to further a diagnosis, assess the severity or extent of a disease, or monitor response to treatment)
- The nature of the proposed investigation
- Any risks that may be involved

9. Encourage feedback and invite questions

I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Seek consent

Remember that you are explaining the reason for an investigation and not telling a patient they must have it. Following explanation, you should seek informed consent to proceed.

Discussion

An 86-year-old woman with moderately severe dementia has a suspicious lesion on chest X-ray. Would you recommend bronchoscopy?

Guidelines for investigating and treating suspected lung cancer suggest bronchoscopy or percutaneous biopsy to guide appropriate treatment – surgery, chemotherapy, radiotherapy or palliation. But guidelines often fail to address significant comorbidity. Here, assessment of cognition, functional and social support and symptom control are likely to supersede attempts to confirm a diagnosis, but investigation may be warranted if likely tumour-related symptoms develop to allow more secure planning of palliative measures. Her capacity to understand the issues should be explored, ideally in the presence of next of kin, and empirical treatment considered if she does not accept investigation. If she accepts investigation, the least likely to cause distress should be arranged, for example a computed tomography scan rather than bronchoscopy.

What do you understand by the terms sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)?

Sensitivity and specificity are to do with finding or not finding disease. Sensitivity is concerned with finding disease, and specificity with not detecting disease in those without the disease. Disease positives and negatives are based on 'gold standard tests' (ultimate diagnostic tests as the profession sees them). Predictive values are to do with diagnostic/screening tests. If a test is positive, the question is whether or not it is good at detecting disease; if a test is negative, the question is whether or not it is good at not missing disease. Sensitivity and specificity are not affected by the prevalence of a disease; predictive values are (Table 4.1).

Sensitivity

Sensitivity refers to the ability of a test to detect disease. It considers all with disease (disease positives) and is the proportion of true disease positives (a + c) that the test detects (a). A highly sensitive test is able to detect disease or target substance in trace amounts and so misses few that have the disease, i.e. a low false-negative rate. For example, bone marrow aspiration and soluble transferrin receptor assay are highly sensitive tests for confirming iron deficiency, whereas ferritin may be misleading.

Specificity

Specificity refers to the ability of a test to exclude disease. It considers all without disease (disease negatives) and is the proportion of true disease negatives (b + d) that the test correctly identifies as negative (d). A highly specific test is able to detect a single disease or target substance and no other and seldom misdiagnoses disease, i.e. a low false-positive rate. For example, mammography screens a defined age population with higher specificity for detecting breast cancer. Lowering the age threshold for screening may lower specificity and increase false-positive results, as younger women tend to have lumpier breasts.

Positive predictive value (PPV)

PPV considers all who test positive and is the proportion of people with a positive test (a + b) who have the disease in question (a). A high PPV is desirable for diagnostic tests, i.e. a low false-positive rate.

Negative predictive value (NPV)

NPV considers all who test negative and is the proportion of people with a negative test (c + d) who do not have the disease in question (d). A high NPV is desirable for diagnostic tests, i.e. a low false-negative rate.

Explain the terms pre-test probability and post-test probability

Pre-test probability refers to the proportion of people with a target disorder in the population at risk and is simply

Table 4.1 Sensitivity, specificity and predictive values

	Disease positive	**Disease negative**	
Test positive (abnormal)	a	b	PPV = a/(a + b)
Test negative (normal)	c	d	NPV = d/(c + d)
	Sensitivity = a/(a + c)	Specificity = d/(b + d)	

NPV, negative predictive value; PPV, positive predictive value.

another term for prevalence. Pre-test probability may be calculated using the formula $(a + c)/(a + b + c + d)$. Post-test probability refers to the proportion of patients with a particular test result who have the target disorder.

What criteria are important in determining whether or not to implement a screening test for a disease?

Ideally, the disease should be common, important and diagnosable by an accepted method. There must be a latent interval between disease onset and important manifestations during which effective intervention is possible. The screening test should be simple, cheap (cost effective) and performed on a group deemed by policy to be at high risk. It should have a high sensitivity and a specificity.

What is meant by a valid and reliable test?

A valid test is one that measures what it sets out to measure. A reliable test is one that produces repeatable results.

Which factors may influence a decision to investigate older people?

Guidelines for investigating conditions can fail to address individual factors that should be considered when assessing the potential benefits and risks of investigation; such factors become more common with advancing age. Comorbidity and multiple pathologies become more likely in older patients, with an increase in chronic diseases, and it can be more appropriate to identify problems and use problem solving than seek single unifying diagnoses, and more appropriate to make judgements as to which problems are most probably affecting quality of life. Cognitive impairment, either mild or dementia, may preclude informed consent for an investigation. Physical disability such as osteoarthritis can, for example, thwart exercise stress testing. Patients' views and wishes are of course most valuable in deciding the best way forward. A common example is the extent to investigate anaemia in an older person once a basic 'blood screen' has been completed.

A pragmatic way of decision making for investigating older people is to select investigations most likely to change management or yield prognostic information. If a patient is competent to give informed consent to an investigation then it is possible to proceed; if not then it may be discussed with those close to the patient, and a decision made in the patient's best interests as judged by the doctor. If either a competent patient or those close to a patient not competent refuse investigation then empirical treatment might be offered.

Automatic investigations that will not benefit patients are inappropriate but discrimination against older patients by restricting access to investigations is equally unacceptable. Decisions should be made by balancing potential benefits and risks, and not determined by age.

CASE 4.3 DISCUSSING TREATMENT

Candidate information

Role

You are a doctor on the cardiology ward.

Please read this summary.

Scenario

Re: Mr James Bonde, aged 80 years

Mr Bonde is recovering well from a non-ST elevation myocardial infarction. Although well before admission, coronary angiography is not being considered and he is keen to go home. He is currently taking aspirin. Beta blockade is deemed risky on account of sinus bradycardia. His blood pressure is 160/90. You think he might benefit from clopidogrel, a statin and an angiotensin-converting enzyme inhibitor to further modify risk.

Your task is to explain these treatments to him, and allow him to make an informed choice about whether or not to take them.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr James Bonde is an 80-year-old man who has never before been in hospital. He was admitted to hospital 4 days ago with a heart attack. His wife died of heart disease 6 years ago, having taken many medications for her heart. He feels he has had a good life. He does not want to be kept in hospital for further tests or treatments if he can be allowed home more quickly without these, and fully accepts he might be declining potentially optimal, 'cutting edge' approaches. He feels simply that he has done all that he wants to in life and 'will accept the end when it comes, with or without treatment'. He will consider treatment that keeps further chest pains at bay, but does not want 'anything too complicated'.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Explain the reasons for considering treatment

I'm glad to see that you are recovering from your recent heart attack. Your test results are largely encouraging but your blood cholesterol level and blood pressure are still a little high. When the cholesterol is high and we don't treat it, this can increase the risk of future heart attack, as can high blood pressure. Fortunately, the risk can be reduced with medication and I think we should discuss starting this medication in your case.

3. Give the patient a chance to react to the need for treatment

Remember that a lot has happened to him recently. His world has been changed by the heart attack. He probably had an enormous fright when admitted, and is still coming to terms with the repercussions of his diagnosis. He will have received a great deal of advice from doctors, nurses and members of the cardiac rehabilitation team. He will be on a range of tablets indefinitely. It is important to recognise that his hopes and yours may not immediately be the same. There may be a mismatch of agendas. You want him to start more tablets and then see your next patient but he desperately wants some good news. Yet more tablets may not be what he had in mind. Going home may be. Give him a chance to react to what you see as the most important next step, and appreciate his.

4. Be alert to ideas, concerns and expectations

Establishing prior experience (e.g. of his wife) can help you understand any specific beliefs. Throughout your explanation, try to take account of any ideas, concerns and expectations you elicit.

5. Explain the likely benefits of treatment

Explain these as accurately as possible, without overwhelming him with outcomes of studies. It often helps to reassure patients that others are taking the same drug and that your advice is commensurate with the larger body of current medical opinion.

6. Explain what the treatment involves

Explain the frequency of dosing of tablets, the duration of therapy and any special instructions (e.g. when tablets should be taken). Any requirements for blood monitoring, if relevant, should be discussed.

7. Explain likely side effects of treatment

Mention side effects that are common or serious. Try to explain the balance of risk (benefits versus side effects). Explain what should be done if a side effect occurs. Many patients know that aspirin can cause ulcers, but carry on taking it if they have bleeding symptoms. Patients have not worked in medical units. Do not assume that what is obvious to you is obvious to your patient.

8. Encourage feedback and invite questions

I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

9. Seek consent

Remember that you are explaining the reasons for tablets and not telling him he must have them.

10. Respect autonomy

Ultimately, the decision to accept treatment or stay in hospital is his, and his informed decision should be respected.

Discussion

Are you more reluctant to prescribe medications for older people?

Treating older people must aim for maximum benefit (it is older people who often derive most benefit from a particular drug) and minimal adverse effects by avoiding excessive or inappropriate medications. To achieve this balance, individualised prescribing that considers comorbidity, co-prescription and social aspects of care, and careful judgement of overall frailty and likelihood of benefit, are crucial. Older people are often inappropriately under-represented in therapeutic trials, and so the size of benefit might be underappreciated in an older person, but so might the absolute risk increase. Six rules in prescribing for older people are shown in Box 4.3.

Is drug treatment for coronary syndromes the same for older as younger patients?

Thrombolytic agents provide a greater absolute benefit in older people and should only be withheld if there are contraindications, although these are more likely in older people. Meta-analyses of aspirin trials show around 25% reduction over 2 years in secondary prevention of major vascular occlusive events, relative risk reduction being similar in younger and older people but absolute benefit greatest for high-risk patients over 65 years (but the risk–benefit ratio tips aspirin out of favour for low-risk older people in primary prevention). Beta blockers after myocardial infarction reduce mortality from ischaemia and arrhythmias with evidence up to 75 years, but beyond this age benefit can only be extrapolated and older people are more likely to have relative or absolute contraindications, such as sinus pauses or postural hypotension. Angiotensin-converting enzyme inhibitors reduce mortality and morbidity in cardiovascular disease but again older patients are more likely to have contraindications such as hypotension, moderate aortic stenosis or vulnerable renovascular disease.

Is treatment for hypertension the same for older as younger patients?

Absolute benefit from antihypertensive treatment is much greater in older people.

Is treatment for hyperlipidaemia the same for older as younger patients?

The benefits of statin therapy are deduced from overall risk rather than lipid concentration. The Heart Protection

Box 4.3 **Prescribing for older people**

1. Consider the indication

This includes stopping drugs when investigations do not support a diagnosis. It is not uncommon for patients whose results do not support ischaemic heart or other vascular disease to be continued on antiplatelet, antihypertensive or lipid-lowering treatment and to be re-admitted with anaemia or hyponatraemia.

2. Be alert to possible side effects and limit prescribing

Almost any drug can provoke confusion. Extrapyramidal side effects are not uncommon with antipsychotics, anti-emetics and anti-histamines; depression can be triggered by beta blockers and calcium channel blockers; constipation can be the result of opiates, diuretics and anticholinergics. Broad-spectrum antibiotics, antipsychotics, benzodiazepines, beta blockers and phenytoin are just some drugs that may be better avoided in older people.

3. Do not withhold treatments that work

Warfarin, for example, is often inappropriately withheld. Osteoporosis treatment is underprescribed.

4. Stop inappropriate medications

The aim should be symptom relief, for example in patients who are dying, who should not be given a diet of drugs to prevent vascular disease.

5. Be imaginative with routes of administration

Use intramuscular gentamicin, for example, in an agitated, confused patient with a urinary infection.

6. Consider concordance

Ideally patients should be discharged with a list of their treatments and the reasons for each.

Study showed significant reductions in first event rates (around 25%, $P < 0.0001$) for myocardial infarction and stroke each year after the first year and these rates were similar in those under or over 70 years. Statins should be considered for patients with occlusive arterial disease or diabetes where life expectancy is greater than 1 year and quality of life is positive.

Is warfarin justified in patients aged over 75 years with atrial fibrillation?

Warfarin in atrial fibrillation reduces stroke risk by 68%, compared with 21% with aspirin. The high rate of intracranial haemorrhage with warfarin in patients aged over 75 years does not negate its benefit, but comorbidities limiting life expectancy may limit its potential benefit.

What do you know about drug-induced disease?

Any drug may cause disease, and drugs should always be included in the differential diagnosis of symptoms. For example, a glance at the drug chart might reveal the concomitant use of a selective serotonin reuptake inhibitor (SSRI), a tricyclic antidepressant and tramadol; SSRIs are enzyme inhibitors that enhance the action of the other drugs and the combination of a SSRI and tramadol can produce a serotonergic syndrome. Common drugs causing disease include non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, clopidogrel, warfarin, diuretics, angiotensin-modifying agents and corticosteroids, but these drugs are commonly prescribed. Over-the-counter drug use should also be explored, as around 25% of hospitalised patients may be taking these yet in only around 1% of patients do they appear in their case records.

What do you know about adverse drug reactions (ADRs)?

ADRs are a challenge for both primary and secondary care, and reflect the value of a strong pharmacist presence in the health-care team. Year on year drugs are withdrawn because of safety concerns, examples in recent years including cerivastatin, rofecoxib and co-proxamol; 6.5% of hospital admissions are due to ADRs, and 14.7% of patients experience an ADR in hospital, a major proportion of these thought to be potentially preventable. Drugs should thus always be considered in the differential diagnoses of presentations. To assess cause and effect may require any of a temporal relationship, re-challenge, exclusion of other causes, novelty or de-challenge (dose reduction or withdrawal). Errors in omission appear to be more common than commission. Alternative medicines are a large problem, and for example ginseng, feverfew and garlic reduce platelet function and St John's wort induces drug metabolism of protein pump inhibitors and this combination may result in gastric bleeding. The Medical Research Council for Drug Safety Science Hospital Admission Study revealed the top 10 causative drugs for ADRs as NSAIDs, diuretics, warfarin, angiotensin-converting enzyme inhibitors, antidepressants, beta blockers, opiates, digoxin, prednisolone and clopidogrel. NSAID-induced peptic ulceration is the most frequent ADR cause of admission. Antiplatelet agents are a common example of the benefit–harm balance consideration, as they benefit vascular disease but may cause gastrointestinal bleeding, the latter risk increased with NSAIDs and former benefit reduced by some gastroprotective agents.

Are pharmaceutical companies and pharmaceutical representatives to be considered favourably by doctors?

Absolutely, and yet doctors are often naive as to how drugs must be developed, licensed and marketed. The pharmaceutical industry is an essential one of scientists, health-care professionals and business people without which we would have no drug development, no drug trials and no drug information with and upon which to treat our patients.

What do you know about drug licensing?

Drug licensing is not able to influence the vigilance all doctors must have to licensed drugs, but is a vital line of defence against drug-induced disease. The *British Medical Journal* in 1909 published a report on 'Beechams Remedies', a popular product at the time which falsely claimed a dazzling range of benefits, but which contained little else than soap and ginger. Licensing became formalised in 1958 in the thalidomide era, and now to gain a licence a drug must pass the hurdles of quality of manufacture, efficacy in the proposed indication and reasonable safety. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, through its Commission on Human Medicines and Licensing Authority, has a pivotal role. On introduction, most drugs go through the phases of initial high expectation then subsequent disappointment before finding their balanced place. Drugs then generally have a period of patency protection before coming 'off-patent' and becoming generic, whereupon 'me-too' products at competitive rates may consume 90% of sales. Pharmaco-vigilance is vital, and MHRA pharmaco-vigilance groups receive yellow cards from reporting doctors, and these provide vital cumulative clues of danger; not enough doctors submit these.

CASE 4.4 DISCUSSING MANAGEMENT, PROGNOSIS AND POSSIBLE COMPLICATIONS IN A PATIENT WITH MULTIPLE PROBLEMS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

Re: Mr John Rowe, aged 76 years

Mr Rowe had a partial gastrectomy for gastric cancer 2 years ago. It was diagnosed very early, by oesophagogastroduodenoscopy for dyspepsia. After surgery and a course of *Helicobacter pylori* eradication he had no further symptoms and his surgeon told him all appeared to be clear. He now has recurrence of dyspepsia and is seeing you urgently in clinic and wants to know if the cancer might have returned. He has recently seen the cardiologists because of suspected angina and awaits angiography. He has been started on aspirin, a statin and an angiotensin-converting enzyme inhibitor but not a beta blocker on account of mild chronic obstructive pulmonary disease for which he takes inhalers. He also wishes to talk to you about his angina and breathing because he feels the cardiologists did not tell him very much. And he has recently had two episodes of fresh rectal bleeding, but he is not too troubled by this. You may assume systematic enquiry otherwise unremarkable.

Your task is to address his concerns and discuss a way forward.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr John Rowe is a 74-year-old man who had an operation for gastric cancer 2 years ago. It was diagnosed very early, by investigation for ingestion. After surgery he had no further symptoms and his surgeon told him 'all was clear.' He now has recurrence of indigestion. He has also recently seen the cardiologists because of suspected angina and had a positive exercise tolerance test and awaits angiography. He has been started on aspirin, simvastatin and ramipril. He has mild emphysema for which he takes inhalers, and gave up smoking 20 years ago. He also wishes to talk about his angina and breathing because he feels the cardiologists did not tell him very much. He is worried about the risks of an angiogram but also worried that without further tests he could have a heart attack. He wonders what his risk of a heart attack might be. He recently had two episodes of fresh rectal bleeding, but is not too troubled by this.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Know how to deal with multiple problems

It is increasingly common in general internal medicine to face numerous problems in a single consultation. Patients with multiple problems are often uncertain about what is really wrong. They might not know why certain tests are being arranged. They might not know exactly why they are taking medications. And in the era of increasing specialisation they might be attending multiple specialist clinics, sometimes punctuated by acute admissions to hospital after which they are discharged on different tablets, and they might have difficulty organising and retaining sometimes seemingly conflicting advice from the different health professionals they have seen.

3. Take one step at a time

Your task is to arrange the puzzle into a series of boxes, and address each of these on the basis of which you see as priorities. In this case an appropriate way forward is to address the dyspepsia first and consider further endoscopy (which he has had before), and reassure him that you will move on to discuss his angina and breathing problems afterwards, and not forget his rectal bleeding.

4. Obtain the facts

Dyspepsia is often hard to differentiate from cardiac chest pain. He has cardiac problems but equally a history of gastric malignancy and recently starting aspirin and so has two compelling reasons to proceed to oesophagogastroduodenoscopy (balanced against minor procedural risks posed by stable angina).

5. Explore concerns

Make sure you explore any specific concerns he may have, for example about proceeding to the angiogram.

6. Discuss management options with a clear framework

> I think we should strongly consider looking into the stomach again with the endoscopy you had before. This will tell us quickly whether or not there is anything we need to be worried about. I'd hope it would simply show some ulceration that we can treat with tablets, and this would not be uncommon in people taking aspirin. But I think you should continue the aspirin for the time being, as it gives some protection to the heart. In the unlikely event that the endoscopy showed anything more untoward then we would be in a better position to know what to do sooner rather than later.

7. Discuss potential prognoses and possible complications of any diagnoses (with and without treatment) or treatments

It can be easy to be drawn into discussion of possible outcomes but as far as possible try to avoid hypothetical discussion of what has not been diagnosed. With respect to his angina, it would be best to leave management in the hands of the cardiologists, but appropriate to comment on the reasons for angiography (to consider if a procedure such as stenting would help his angina) and the importance of medications in reducing the risk of a heart attack.

8. Prioritise … but do not forget unturned stones

It is important at this stage not to ignore his rectal bleeding, which he considers less important. But unturned small stones can sometimes turn out to be very significant.

> I do not think we should ignore the bleeding you have had from the tail end, and it may be preferable for us to consider examining the tail end with a flexible telescope with a light on the end – similar to the endoscopy you have had before – to be certain we are not missing something.

Assuming rectal examination normal, colonoscopy might be a crucial test, and the decision is where to place it in the overall sequence. One way forward would be to request it provisionally (waiting lists will preclude rapid access!).

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

Box 4.4 **Issues to be aware of in managing older people**

- **R**educed body reserve
- **A**typical presentations
- **M**ultiple problems/pathologies
- **P**olypharmacy
- **S**ocial adversities

10. Agree a way forward and ensure follow-up arrangements are in place

Reassure him of follow-up arrangements, and that you would happily review sooner at any time at his or his general practitioner's request if there are questions or concerns.

Discussion

What issues should you be generally aware of when managing older people?

Many of the scenarios in this book deal with older patients, and appropriately so since general internal medicine is managing an increasingly older population. A mnemonic for issues you should be particularly aware of is given in Box 4.4.

CASE 4.5 DISCUSSING DIAGNOSTIC UNCERTAINTY

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

Re: Miss Melissa Hamilton, aged 24 years

You have been seeing Miss Hamilton in clinic for follow-up of Crohn's disease. She has been asymptomatic for 6 months. At the end of the consultation she mentions that she has had pain in her right calf for the past week. She hoped you might take a quick look at it. Examination is unremarkable.

Your task is to discuss management options with her.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Miss Melissa Hamilton is a 24-year-old woman with Crohn's disease that has been well controlled on treatment for 6 months. At the end of her outpatient consultation she mentions that she has had pain in her right calf for the past week. She didn't want 'to bother her GP' and hoped you might take a look at it. She is not particularly concerned about it but wonders what it might be due to. She is otherwise well. She started the combined oral contraceptive pill (COCP) 2 months ago whilst touring in Australia with her boyfriend. They returned home 10 days ago. She has no family history of thromboembolic disease.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Clarify the task

Confirm that the problem is calf pain, and nothing else.

3. Obtain the necessary facts

Gather information that is necessary to discuss management. Crucially, this includes additional symptoms and risk factors for venous thromboembolism – personal or family history, long-haul travel, COCP.

4. Be alert to ideas, concerns and expectations

She probably has no concerns about a deep venous thrombosis (DVT).

5. Outline the possibilities

She appears to lead an active lifestyle, has no signs of a DVT, and the absolute risk of thromboembolic disease on the COCP is very low. Conversely, she has two possible risk factors, the COCP and a long-haul flight, and thromboembolic disease, although unlikely, can be life-threatening and is treatable.

6. Share the probability and potential seriousness of a diagnosis

Probability is discussed in Box 4.5.

> This is most likely harmless muscle pain. There is a small possibility the pain is due to a clot of blood in one of the deeper veins of the leg. It is difficult to exclude this without further tests. Although I think a blood clot very unlikely, there is a risk that an untreated blood clot could travel to the lungs and cause serious harm. We could arrange a blood test and then possibly a scan of the leg to be more sure, if you wanted us to.

This sounds straightforward, but in practice there can be a problem with sharing information in this way. Patients frequently do not warm to the idea of being asked to make a decision and 'if you wanted us to' may be too open ended to actually help her decide. She might respond:

> Well, you're the doctor, I'll take your advice. Do you think it's really necessary?

Sharing information is more than showing patients the menu!

Box 4.5 **Probability and potential seriousness of diagnosis**

A symptom may have a low probability of representing serious pathology but a high probability of serious consequences if ignored. Such information should always be shared with a patient. The management of disease in theory is often clear cut: investigation A for suspected disease B; treatment Y for disease Z. In practice, whether or not to embark on an investigation in the face of limited evidence is a complex decision that should involve sharing your knowledge, concerns and expectations with the patient.

7. Give an honest professional opinion

If these decisions are difficult for us, with medical training, then they can be enormously difficult for patients, given only small quantities of distilled information. Since there is no clear history of muscle strain, the potential seriousness of a DVT may persuade you to say:

> I'd advise a blood test called a D-dimer. If this is negative we can be reassured that a blood clot is highly unlikely. If it is positive, we should go on to arrange a scan of the leg to be sure.

8. Confirm understanding

It can sometimes be useful to ask the patient to recount what they feel to be the important points of the discussion.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Cast a 'safety net'

If a patient decides not to pursue tests, always have a safety net, such as follow-up by the general practitioner or to seek medical advice if symptoms develop further. Any decision that involves waiting for something else to happen before acting should be 'safety netted' and patients should be clear about which symptoms should prompt reassessment.

Discussion

An 85-year-old man has had a large cortical stroke causing dysphasia and dense hemiplegia. Routine tests reveal a haemoglobin of 9 g/dl with a low ferritin. Would you investigate this further or accept diagnostic uncertainty?

Oesophagogastroduodenoscopy (OGD) and colonoscopy are the standard investigations to look for a source of chronic blood loss in iron deficiency anaemia. However, the balance of risk of proceeding with these might not be in the patient's best interests immediately. OGD might increase the risk of hypoxia, colonoscopy impractical and depending upon the type of dysphasia informed consent could be an issue. Investigations should probably be delayed until the outcome of the stroke is clearer, and as an interim measure exclusion of other haematic deficiencies, supplemental iron and possible withholding of antiplatelet treatment is appropriate. If recovery is satisfactory investigations could be instituted a few weeks later, and even if colorectal cancer is diagnosed and inoperable or declined because of operative risk, then such information may influence placement or the type of future care provision. If there is severe residual disability from the stroke, then investigations should probably not be pursued and perhaps only considered if severe blood loss demands repeated transfusion. Myelodysplasia is common in older people and anaemia is not usually a contraindication to antiplatelet therapy if monitored closely, or even anticoagulation if there is an embolic source and high risk of further stroke in a recovering patient.

A 70-year-old woman has new onset exertional chest pain. She has severe osteoarthritis, walking only a limited distance, and Parkinson's disease. Would you attempt to further the diagnosis of angina with a stress test?

A stress test could define risk more precisely and identify whether coronary angiography and potential revascularisation is likely to be of benefit. Pharmacological testing with dipyridamole, dobutamine or adenosine would be needed. The likely net befits of investigation and possible treatments should be explained and her views sought as to whether to proceed to testing or a more conservative strategy.

A 48-year-old non-smoker is being discharged from your ward today following investigation for chronic diarrhoea. No cause has been found. He tells you that a few weeks ago he had a single episode of 'coughing up a teaspoonful of blood' that he'd forgotten to mention until now. His chest X-ray was normal. What are the important issues?

There is probably no sinister cause. It has not recurred and he is a non-smoker with a normal chest X-ray. Nevertheless, the haemoptysis remains unexplained. There are numerous potential approaches to the problem. At one extreme he might be reassured and told that no further tests are needed; at the other extreme he could be advised to have a bronchoscopy to exclude a tumour. Each doctor has his or her own 'risk threshold' for undertaking investigations, but the problem with each is that they do not involve the patient. It would be important to share with him that a small lesion may not show up on chest X-ray and that the only way to be certain of excluding this would be with further tests. Teamwork is integral to good clinical care and when you feel out of your depth in making a decision then you should seek advice.

CASE 4.6 DISCUSSING RISK AND TREATMENT EFFECT

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

> Re: Mr Christopher Roberts, aged 47 years
>
> Mr Roberts was admitted with atypical chest pain and is about to be discharged on a statin because of a cholesterol level of 6.5 mmol/l. He is obese with a body mass index of 32, and has numerous other risk factors for cardiovascular disease (CVD) including smoking, alcohol consumption on the edge of safety and borderline hypertension. You are aware of evidence that stopping smoking, statin therapy, targeting his hypertension (alcohol reduction playing a part), exercise and a 'Mediterranean' diet will significantly reduce his relative risk of CVD and developing type 2 diabetes.
>
> Your task is to discuss his perceived risks and the benefits of these treatments and lifestyle modifications with him.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Christopher Roberts is a 47-year-old travel agent admitted with chest pain initially thought to be angina. He is very relieved to be told that investigations have not shown evidence of a heart attack or angina and that his pain is now thought to be muscular resulting from poor posture and a sedentary lifestyle coupled with a lot of driving and a recent minor whiplash accident. He is about to be discharged on a statin because of a cholesterol level of 6.5 mmol/l. He is obese, with a body mass index of 32, and has numerous other risk factors for coronary heart disease including smoking, 42 units of alcohol per week and high blood pressure. His father died of a heart attack at the age of 55.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Review the history

Recap to him that the tests did not show that he had had a heart attack but that it was very clear on assessing him that he had significant risk factors for heart disease.

3. Clarify the task

Make it clear that reducing his risk of future heart attacks is the aim of the discussion, and that this is a very achievable goal.

4. Be alert to ideas, concerns and expectations

That his father died relatively young from a heart attack may be very much on his mind, but he may not know that it puts him at increased risk or that overall risk relates to the interplay with other, modifiable risk factors. Risk perception is discussed in Box 4.6.

5. Clarify risk

Having established his risk perception, clarify exactly what his risk factors are – smoking, alcohol, deficient exercise, high cholesterol and blood pressure – and potential health consequences of these.

6. Risk communication

Frame advice around the benefits of risk modification (Box 4.7).

7. Optimise the likelihood of concordance

Concordance is more likely when risk perception is realised, and he realises risk can be modified and that he can do it. The message can be reinforced through gentle repetition and a plan of action and support.

8. Confirm understanding

Confirm his understanding not just that he is at risk but that his risk can be substantially reduced.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward and ensure follow-up arrangements are in place

This might include writing to his general practitioner and suggesting follow-up with the practice nurse, seeing a dietitian and attending a smoking cessation advice service.

Box 4.6 **Risk perception**

- Risk perception can determine risk-reducing behaviour. People who *perceive themselves at increased risk of coronary heart disease are more likely to adopt risk-reducing behaviours* such as smoking cessation, eating a Mediterranean diet, increased exercise and taking medication. Risk perception consists of two judgements, the *perceived likelihood* of an event and the *perceived severity* of that event.
- Risks can be discussed in verbal categories, such as likely, probable and possible, and in absolute probabilities, such as a 10% chance of having the event. Verbal categories mean different things to different people. *People tend to downplay risk and make overly optimistic judgements of risk in comparison with others of the same age and sex.*
- The *perception of being at increased risk is unlikely to motivate people to adopt risk-reducing behaviours.* It is *also necessary to perceive that one has control over the risk* of an event and this has two components – *response efficacy* is the perception that risk-reducing behaviour will be effective and *self-efficacy* is having confidence in one's ability to adopt it.

Box 4.7 **Risk communication**

Risk communication involves sharing information about risk, how to reduce it and ensuring that patients have the confidence to change their behaviour.

Response efficacy

It is helpful to outline not just the benefits in terms of coronary heart disease, but also the more widespread benefits of disease-modifying behaviours.

- Stopping smoking will of course also reduce respiratory disease and exercise intolerance and be financially advantageous.
- Statin therapy has well-established primary and secondary preventive outcome benefits.
- Targeting hypertension reduces stroke, coronary heart disease, renovascular disease and peripheral vascular disease.
- Exercise not only reduces the risk of vascular disease but also improves physical dexterity and overall well-being.
- A Mediterranean diet produces similar benefits.

Self-efficacy

Habits are hard to break. Patients must not only be aware of the benefits of trying to improve their situation, but also should be instilled with the belief that they can. Motivation can be assisted by trying to identify which consequences of failing to modify behaviour resonate most with a patient (e.g. not being able to walk into the garden without feeling breathless by the age of 55, erectile dysfunction) and support networks and agencies to assist, such as specialist cardiac and respiratory nurses, smoking advice services and so forth.

Discussion

What is meant by the term prevalence?

This refers to the proportion of individuals in a population with the condition of interest at a point in time.

Prevalence = number with the condition / number in the population

What is meant by the term incidence?

Incidence is concerned with the rate of new occurrences. There are three principal measures of incidence – *risk*, *odds* and *rate*.

What is meant by the term risk?

Risk is simply the *proportion* (a 1 in 2 or 50% chance of a coin landing heads or tails) of disease-free individuals who develop the condition during the study period.

Risk = number of new cases in the period / number of disease-free individuals at the start

It is the probability that a disease-free individual will develop the disease over the period.

What is meant by the term odds?

This is the *ratio* (a 1 to 1 odds of the coin landing heads or tails) of the probability of getting the disease to the probability of not.

Odds = number of new cases in the period / number who remain disease-free during the period

Odds against disease simply inverts the formula.

If 20 people have a stroke out of 100 in a population studied (i.e. 80 do not), the *risk* of stroke is 20 / 100 = 0.2 or 20% and the *odds* of a stroke is 20 / 80 = 0.25 or 25%. We could also think of odds as 'this versus this' and risk as 'this versus the whole population'.

What is meant by the term rate?

Risk and odds assume that all individuals are present throughout the period. In practice, some enter after the start and some leave before the end.

Incidence rate = number of cases / total person time at risk

What is meant by the term risk ratio?

Risk ratio is also referred to as *relative risk*.

Relative risk = risk in exposed group / risk in unexposed group

The risk of an event in an exposed or intervention group is sometimes called the experimental event rate (EER). The risk of an event in the unexposed or control group is sometimes called the control event rate (CER). Assume the risk of myocardial infarction in those treated with lipid-lowering therapy is 1 in 100 (EER) and the risk in the control group is 2 in 100 (CER). The relative risk of myocardial infarction with treatment is (1 / 100) / (2 / 100) or 0.5. Equally, the risk without treatment is doubled or 2.

What is meant by the term odds ratio?

Odds ratio = odds in exposed group / odds in unexposed group

What is meant by the term rate ratio?

Rate ratio = rate in exposed group / rate in unexposed group

If these ratios are 1 there is no difference between exposed and unexposed groups. If <1, the exposed group is at lower risk, and if >1 at higher risk.

How does relative risk (RR) differ from absolute risk (AR)?

Absolute risk refers to the risk difference between exposed (e.g. treated) and unexposed.

Risk difference = risk in exposed group – risk in unexposed group

similarly:

Rate difference = rate in exposed group – rate in unexposed group

These absolute measures are generally referred to as measures of *attributable risk*.

Relative risk should be interpreted in the context of the prevalence of the condition in question. If, for example, a study showed that the risk of a disease x were doubled by a particular drug y (e.g. the risk of venous thromboembolism is increased by hormone replacement therapy), then it is important to place that increased risk in the context of the likelihood of an event (absolute risk). If the natural prevalence or absolute risk of disease x is 1 in 1 million, then the absolute risk in the presence of treatment y is still only 1 in 500 000. A decision to treat will depend upon the risk–benefit ratio of treatment y.

Conversely, relative risk may not, at first sight, seem high, but 10 extra strokes per 1000 people, for example, would be clinically substantial.

What is meant by the term relative risk reduction (RRR)?

RRR is an illustration of how the risk of an event has been reduced by intervention.

RRR = 1 – RR

If, for example, RR = 0.2, then RRR = 1 − 0.2 = 0.8 or 80%.

What is meant by the term absolute risk reduction (ARR)?

ARR refers to the number of additional people who benefit from an intervention out of 100 and is the absolute arithmetic difference in rates of bad outcomes between control and experimental groups in a trial. ARR is therefore useful in determining whether the RRR is important. If CER = 2% and EER = 1%, ARR is therefore 1% and so 1 in 100 people benefit from treatment. If the CER is much smaller, say 0.001%, the ARR achieved by the same RRR of 50% is 0.0005%. This ARR would warrant a much higher 'number needed to treat'.

What is meant by the term number needed to treat (NNT)?

NNT refers to the number of patients who need to be treated to prevent one bad outcome (or achieve one additional favourable outcome and benefit one additional patient). NNT is the reciprocal of ARR, i.e. 1/ARR.

What is meant by the term number needed to harm (NNH)?

NNH refers to the number of patients who need to be treated to cause one bad outcome. The lower the NNH, the more harmful is the treatment.

CASE 4.7 NEGOTIATING A MANAGEMENT PLAN FOR A CHRONIC DISEASE/LONG-TERM CONDITION

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Henry Jackson, aged 45 years

Mr Jackson was admitted with a large anterior myocardial infarction and subsequent heart failure, requiring initial ionotropic support. His echocardiogram showed moderate systolic dysfunction and angiography a critical lesion in his left anterior descending artery for which he received percutaneous coronary intervention. He has been established on numerous secondary preventive drugs (aspirin, clopidogrel, a statin, an angiotensin-converting enzyme inhibitor, a beta blocker and eplerenone). He is being discharged and has some concerns about going home.

Your task is to discuss his concerns and negotiate a management plan for him following discharge from hospital.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Henry Jackson is a 45-year-old man admitted 14 days ago with a large anterior myocardial infarction. He was very unwell for the first few days, and developed subsequent heart failure. He has had a stent inserted in one of his coronary arteries. His echocardiogram shows that he has significant damage to the left ventricle. He is now taking six different medications. He is very concerned that he still cannot walk far around the hospital without feeling a little short of breath. He wonders if he will get back to a normal life. He is very concerned that he was a previously very well man working as a manager for an IT company. He has a wife and two children and could not afford to give up work. He is a little overweight. He used to smoke 30 cigarettes per day.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Clarify the task

Reassure him that your task and expectation is to guide him back to as normal a life as possible.

3. Establish the facts

In practice you would establish as much history as possible but since your communication skills are being assessed you should explore the concerns as soon as possible.

4. Explore concerns

The key word is *concerns*. It is very easy to assume what a patient's concerns are likely to be and then address assumptions. It is not uncommon to overlook a patient's concerns when giving advice after, for example, a coronary syndrome, as there are standard areas that are usually discussed relating to medications. Patients do not always voice their concerns, thinking the doctor 'too busy' or because they are afraid or simply do not know how to. It is important to ask.

> There are a number of things to explain before you go home, but before we start is there anything worrying you in particular?

Concerns will include return to a normal life, return to work, impact on family life, likelihood of taking tablets indefinitely, whether it could happen again and the way forward from here.

5. Share management options

Patients vary in the extent to which they wish to be involved in management decisions, but most want to be informed of possible options. It is worth stating your position if there appears to be a strongly 'right' option clinically and a patient is not keen to concord (e.g. in taking secondary preventive drugs). Where there is a range of clinically acceptable options you could deploy 'thinking aloud' skills, observing the patient's reactions or asking, encouraging good ideas and gently countering bad ones:

> I wonder…
>
> It might help if…
>
> *I expect that if we…*(never say what will happen, only what seems likely)

Explicit categorisation can help, telling your patient that there are three things, for example, you want him or her to know, and that they are as follows.

6. Frame your suggested management plan

Being patient centred is shepherding rather than abdicating all responsibility for decisions to the patient. As well as exploring concerns, you will have a framework of things you need to discuss that might include reasons for each medication (offering to write these down), need for follow-up (hospital and cardiac rehabilitation nurse) and secondary preventive modifications to lifestyle. Most patients prefer doctors who are open, informative and consider their concerns, but with one proviso – that their doctor appears to be *actively in control of the problem*. A good analogy is with active and passive listening. A doctor who sits forward, makes good eye contact and seems attentive is more likely to inspire confidence than one who sits back and appears uninterested. Equally, a doctor who is actively trying to negotiate the best management strategy through considered, informed discussion is more likely to achieve a better outcome.

7. Respond to patient cues

Throughout, be alert to his reactions or ask what he thinks, encouraging good ideas whilst gently countering bad ones.

8. Confirm understanding

It can sometimes be useful to ask the patient to recount what they feel to be the important points of the discussion.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward and ensure follow-up arrangements are in place

Reassure him of follow-up arrangements with your team, including the cardiac rehabilitation team, that you will contact his general practitioner (GP) about his condition and that you would happily review sooner at any time at his or his GP's request if there were any questions or concerns.

Discussion

What do you understand by the term chronic disease or long-term condition (LTC)?

LTCs generally last longer than a year, are incurable, require ongoing care and often progress. They include diabetes, arthritis, asthma, coronary heart disease and chronic heart failure.

Should LTCs be managed by primary or secondary care?

Integration is crucial! Multiple areas of care have evolved separately in the NHS (primary care, secondary care, outpatient clinics, social care, mental health, intermediate care), but the assumption in the past was that general practitioners would coordinate all care. But an ageing population and proliferation of LTCs make this an increasingly difficult task. Ideally, secondary care admissions should fit as acute episodes within a continuum of care for a chronic process that is integrated between multiple services in close liaison. The three broad contexts of managing LTCs are acute care, disease management (monitoring, treatment adjustments, secondary prevention) and frailty management (recognising when patients, often with multiple LTCs, and often in the last year or two of life, can no longer adapt to their environment).

Is there a role for community geriatricians?

The proportion of elderly people with LTCs and frail elderly is expanding with a predicted doubling of people aged over 80 in the next 20 years.

The increasing cohort of older people and greater survival in older people brings with it a greater morbidity in LTCs often with acute crises prompting admission to hospital. Elderly care expertise in the community clearly helps to prevent hospital admissions to acute hospitals, to provide more treatment in community hospitals, and to maintain people at home with regular review in their locality. It allows advance decisions to be made about the appropriateness or otherwise of admission to hospital in the event of acute illness. It also allows comprehensive assessment of people entering long-term care. Publications such as the Department of Health's *Supporting People with Long Term Conditions*, endorsed by the British Geriatrics Society, make a strong case for the role of geriatricians in intermediate and community care.

Most people with dementia and other advancing LTCs have not given any advanced indication of their wishes in the event of life-threatening illness and whether or not they would wish to be transferred to an acute hospital should they develop pneumonia or other potentially terminal illness. The government's initiative Preferred Priorities for Care (formerly Preferred Place of Care) addresses this, and geriatricians, in consultation with GPs and other health professionals, must ensure these issues are addressed at a stage when a patient's cognitive skills are still intact – at least sufficiently so to discuss with them, their family members and carers potentially predictable problems. This is not to deny at all that many care-home residents may benefit from appropriate interventions, but where capacity is dwindling extreme care is needed by people attuned to the person's needs that their common-law rights are respected, and take priority over defensive actions by care-home managers or deputising services that default to acute hospital admission. If appropriate and timely sensitive discussions and decisions are implemented, and community support is available with geriatrician support, inappropriate admissions to hospital and undue distress to patients and relatives could be avoided; and instead of aiming to achieve admission in less than 4 hours through the emergency department many patients will be better served by advance decisions and community care in a familiar and more comfortable environment rather than the acute hospital.

A major role of day hospitals, where patients could receive low-intensity investigation, treatment and care, was to preserve frail people in the community, but this, sadly, was largely eroded by the advent of private nursing home care.

Are domiciliary visits still important?

Domiciliary visits generally serve one of three purposes – to assess patients too unwell or frail to visit outpatient clinics, to assess patients in their own environment and understand the medical and social context and, rarely these days, to provide the human face of the hospital – seen by many as a place of no return to fear – and reassurance that the aim is to enable rather than be the thin end of the wedge that culminates in nursing home placement.

CASE 4.8 ENCOURAGING CONCORDANCE WITH TREATMENT AND PREVENTION

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

Re: Mr Marc Davey, aged 46 years

Mr Davey was in hospital 2 months ago with severe hypertension (240/120 on admission) and renal impairment. Investigations did not reveal a secondary cause for hypertension and urinalysis revealed isolated proteinuria. The renal team decided against renal biopsy and thought it very likely he had nephrosclerosis from hypertension. He was established on an angiotensin-converting enzyme inhibitor and calcium channel blocker. His electrocardiogram showed left ventricular hypertrophy. His blood pressure on discharge was 140/85 but today in clinic is 180/100. He told the nurse that he has not been taking his medications because he has felt well.

Your task is to discuss ways to improve his blood pressure control.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Marc Davey is a 46-year-old man being reviewed in clinic. He was in hospital 2 months ago with headaches, severe hypertension and resulting kidney damage. Investigations did not reveal a secondary cause for hypertension. He was started on perindopril and amlodipine to control his blood pressure but stopped taking these soon after discharge because he developed an irritating cough. He has felt well since and did not see a need to continue medications. The hospital team had told him it was important to continue taking tablets but he does not remember the reason. He has a wife and two children and enjoys life. He is not overweight, but has successfully given up smoking. He manages a vineyard, but does not consume excess alcohol.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Clarify the task

Make it clear that achieving better control of his blood pressure is the aim of the discussion. Do not assume at the start that you are dealing with poor concordance.

3. Explore whether poor concordance could be a problem

The term concordance is often preferred to compliance since the former suggests agreement between patient and doctor. Concordance should always be checked before evaluating the effectiveness of a treatment. Non-concordance with antihypertensives is common, and it is important not to apportion blame. Patients do not take medications for many reasons and the discussion should begin with this premise and not by highlighting this patient's 'failure'. Before you attempt to influence him in taking his medications, consider the three questions in Box 4.8.

4. Be alert to ideas, concerns and expectations

His cough is probably the result of the angiotensin-converting enzyme (ACE) inhibitor but he may think it a side effect of all antihypertensives. He may, at the time, have appreciated the severity of his illness but may not understand that despite feeling well hypertension could lead to worsening chronic kidney disease and an ultimate need for renal replacement therapy. He may also not understand the other effects of uncontrolled hypertension, notably stroke.

5. Counter misunderstandings

Explain that ACE inhibitors can cause cough, but not amlodipine, and that there are alternatives (e.g. angiotensin receptor blockers). Explain the risks of uncontrolled hypertension.

6. Discuss management options within a clear framework

Frame the discussion around advantages that are likely to be important to him – retarding progressive chronic kidney disease, reduction in stroke risk, need for future hospital admissions and so on. Such *gift wrapping* of treatments can be highly effective. Sometimes illustrating the point with reference to a similar case can help. Explain that all blood pressure tablets can have side effects but that these are usually mild and if problematic a different tablet can always be considered.

Box 4.8 **Questions about concordance**

Are you dealing with poor concordance?

Often the importance of taking medications has not been carefully explained or sufficiently emphasised. Even when explained, patients may still not fully understand or may forget the importance of medication.

Is poor concordance due to iatrogenic symptoms?

Always consider drug side effects or drug–drug interactions as a reason for a patient not taking prescribed medication.

Is the poor concordance due to another reason that needs to be explored?

Very often, poor concordance is due to discrepancy between what the doctor sees as important and what the patient sees as important.

7. Repeat important information

This is especially important when poor concordance may be due to misunderstanding or previous poor explanation.

8. Confirm understanding

It can sometimes be useful to ask the patient to recount what he or she feels to be the important points of the discussion.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward and ensure follow-up arrangements are in place

Reassure him of follow-up arrangements and that you would happily review sooner at any time at his or his general practitioner's (GP) request if there are questions or concerns.

Discussion

A 34-year-old man being treated for a high-grade non-Hodgkin's lymphoma on your haematology ward is 3 days into a chemotherapy regimen involving high-dose steroids. This morning, according to your house officer, he was in a strange mood, tearful but also declaring he believed himself cured. He left the ward in pyjamas and overcoat and has not returned. What should be done?

Patients have the right to decide how they are going to be treated and indeed whether they are going to be treated. Such autonomy should be respected. But where declining treatment is likely to have serious consequences it is imperative to explore a patient's reasoning. Here, iatrogenic mood disturbance from high-dose steroids must be considered, and his 'autonomy' questioned until further assessment has been made. Informing ward staff, the consultant, the patient's GP, relatives, and, on discussion with the consultant, involving hospital security and the police (restraint under the Mental Health Act is generally a last resort but may need to be instituted) are steps which may be needed to ensure his safety.

How might you help persuade a patient to stop smoking?

As well as the serious cardiac, respiratory and neoplastic risks of smoking, it carries considerable social harms and promotes premature ageing. Smoking cessation (Box 4.9) carries immediate benefits, including mortality reduction, and reduces the risk of many diseases including

Box 4.9 Discussing smoking cessation

Ask about current smoking status

This includes asking about whether other household members smoke.

Advise about the benefits of smoking cessation

These include physical, social, financial and cosmetic. Emphasise the health benefits of stopping rather than the risks of continuing smoking. Reinforce the patient's own motivation for wanting to stop.

Ask about reasons for wanting to stop and assess motivation

Ask if the patient really wants to stop and if they would be prepared to stop now or within the next few weeks. Find out about previous attempts to stop and what measures helped or hindered. Ask if other household members are willing to stop, too.

Discuss ways of assisting

These could include setting a date and stopping completely, enlisting the help of family and friends, enlisting the help of health promotion services and GP, nicotine replacement therapy (best avoided in severe cardiovascular disorders) and bupropion (amfebutamone). It helps many patients to consider themselves 'non-smokers' rather than 'ex-smokers'.

cardiovascular disease, chronic obstructive pulmonary disease, cancer of lung, mouth, throat, larynx, oesophagus, pancreas, bladder and cervix, peptic ulcer disease and complications of pregnancy. Nicotine addiction is now acknowledged as a treatable condition and there is substantial evidence of the effectiveness and cost effectiveness of behavioural and pharmacological interventions.

Communication in special circumstances

CASE 4.9 CROSS-CULTURAL COMMUNICATION

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

Re: Mr Ash Khan, aged 38 years

Mr Khan is an asylum seeker. He has been in the UK for 1 year with his family and was referred to your clinic with sweats, fevers and painful joints, although language differences have thwarted some elements of history taking on previous occasions. On one occasion you had an interpreter in clinic but he is not here today. However, Mr Khan's English comprehension has improved steadily over the last year. After extensive investigations he appears to have chronic osteomyelitis of his knee. Tuberculosis has not been suggested by chest X-ray or other results so far.

Your task is to explain the likely diagnosis to him and propose referral to your orthopaedic colleagues for further treatment and possible bone biopsy and surgery.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Ash Khan is a 38-year-old asylum seeker. He has been in the UK for 1 year with his wife and two children and has found work in a restaurant. He was referred to clinic with sweats, fevers and painful joints, although language differences have thwarted good history taking on previous occasions. On one occasion there was an interpreter in clinic but he is not here today. However, Mr Khan's English comprehension has improved steadily over the last year. After extensive investigations he appears to have chronic osteomyelitis affecting his knee. Tuberculosis is possible but not likely on the basis of tests so far. Mr Khan simply wants to be relieved of pain and has been taking a lot of tablets from a local herbalist.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity. Inevitably if there are language differences a consultation has the potential to take longer and ideally in practice (not in PACES) you would allow more time for this.

2. Remember to treat patients equally and do not do very much differently!

When people communicate, there is a vast array of cultural influences. Cultural background, health beliefs and expectations affect all health-care encounters with patients. These differences may seem stark when there is an additional language difficulty, but perhaps most important is to remember that we are usually more similar to each other than we are different! The range of human beliefs, concerns and expectations that we must be aware of with any patient needs to be considered, and perhaps with heightened awareness when treating people from different cultures. Beware of the tendency to stereotype people – to assume they have characteristics because they appear to belong to a certain group. When stereotyped, people can become victims of prejudice – opinions, often unfavourable, formed without good reason. This can jeopardise good care.

3. Establish as far as possible the patient's concerns and give non-verbal reassurance

This patient might simply want to have his pain relieved, and you should indicate that this too is a concern of yours, but that you wish to treat the underlying cause.

4. Frame your suggested management plan

The medical steps are fairly clear – continuing to relieve pain, and urgent referral to orthopaedic colleagues. Sometimes religious reasons mandate an approach to management. During Ramadan, for example, Muslim patients may not eat anything, including tablets, during daylight hours and often eat a large meal after dark. Type 2 diabetes is common in Asian people and if Muslim there may be important repercussions on the style of management chosen.

5. Keep explanations clear and simple, avoiding jargon

The same principles of good communication apply when dealing with patients from different cultures. In other words, you should try to do more of the same, rather than treat such patients differently. In this case, as well as explaining the way forward with respect to input by the knee specialists, you might need to counter the herbal remedy beliefs. You might also need to explore his work further, particularly if tuberculosis is still in question!

6. Repeat important information

This can be particularly important when communicating with people whose first language is not English.

7. Respond to patient cues

Throughout, be alert to his reactions or ask what he thinks, encouraging good ideas whilst gently countering bad ones.

8. Confirm understanding and acceptance

It would be important to ask him to recount what he understands to be the main points of the discussion.

9. Encourage feedback and invite questions

> Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward and ensure follow-up arrangements are in place

Ensure that there are arrangements for treatment and follow-up.

Discussion

What do understand by the term culture?

It refers to the shared beliefs, values and attitudes that guide the behaviour of a social group. It is applied most commonly to describe people of a shared national, ethnic or regional origin, but there is a dynamic social context for every individual's culture that embraces age, gender, education, socioeconomic background, language, family, occupation, religion and so forth.

Box 4.10 **Potential problems when using interpreters**

- Assuming the patient cannot understand any of what is being said – beware of assumptions and seek to find out what a patient can and cannot understand
- Failure to address both the patient and the interpreter
- Failure to communicate simply and in small chunks
- Incorrect understanding or transmission of information
- Avoidance of delicate topics
- Domination of the patient by the interpreter
- Failure to allow enough time (at least a doubling of time is often required)

What potential problems may arise when using interpreters?

These are outlined in Box 4.10.

CASE 4.10 COMMUNICATING WITH ANGRY PATIENTS OR RELATIVES

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Charlie Buchanan, aged 69 years

Mr Buchanan has a left hilar mass on his chest X-ray, discovered during the course of investigations for pneumonia. The computed tomography scan suggests a potentially operable bronchial carcinoma, with lymphoma the main differential diagnosis. Although recovered from his pneumonia, and now feeling well, he was kept as an inpatient because the respiratory team had a slot for bronchoscopy at the end of the week. However, you have now been informed it has been postponed because of a full list of urgent bronchoscopy appointments. You are also aware that the respiratory team is thin on the ground next week because of a conference and have been informed by the respiratory specialist registrar that it will be the week after next. He advises you to send Mr Buchanan home in the meantime. Mr Buchanan is angry.

Your tasks are to listen to his concerns and discuss possible solutions.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Buchanan is a 69-year-old man with possible lung cancer discovered on chest X-ray during the course of investigations for pneumonia. The computed tomography scan suggests a potentially operable tumour. Although recovered from pneumonia, and now feeling well, he was kept in hospital because the respiratory team had arranged his bronchoscopy at the end of the week. However, the respiratory specialist nurse advised him that this has now been postponed and that it might be best if he went home as the respiratory team will not be around next week. Mr Harris does not think he should be told 'what is best for him.' Mr Buchanan lives alone and his son and daughter-in-law are going on holiday next week. He has a history of anxiety and depression and feels that going home without all of this being resolved and without support will be hard. His wife died from oesophageal cancer 2 years ago and he recalls similar delays with her investigations. He is worried that each day missed is a day when the cancer could be spreading. He has always been an avid supporter of the NHS but his support is now beginning to waver and with this news he feels angry. He is particularly upset that the respiratory team are going to be 'sunning themselves' whilst he waits for vital tests.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduce yourself

Introduce yourself and confirm the name/identity of the patient.

2. Make it clear that you want to help

Show from the outset that you are here to try to help. Remain polite. The nature of medical training equips most doctors well with the skills of negotiation. Some patients simply do not have these skills. People are capable of acting out of character and appearing aggressive when upset. His primary motivation is likely to be fear or distress and he is depending on you to help. Do not take any criticisms of the system personally.

3. Remember to deal with emotions before facts and that anger is not usually anger

Always try to calm emotions before dealing with any facts and remember that anger is usually secondary to another emotion such as fear, guilt or uncertainty. Discovering the underlying emotion is far more likely to achieve resolution than taking anger at face value. Since minor disagreement can explode unpredictably into more serious confrontation, dialogue should, from the start, work towards de-escalation and resolution.

4. Acknowledge the concerns

Legitimising rather than confronting his understandable concerns will help bridge the gap between his initial anger and your remit to help:

> Obviously you are very upset by this. I understand.
>
> I can understand fully why you are upset. I am very concerned, too, that you are having to wait.

5. Explore the emotions and concerns

In this case fear of cancer spreading and opening of the old wounds of his wife's experiences will doubtless be forefront in his mind:

> I agree that we must sort this out as quickly as possible. I will do everything I can to help. It will help me if I understand what you fear most if the investigations are delayed.

6. Work towards resolution, weaving in the facts

Steer away from areas of conflict – comments from other staff that may have upset him, for example. Good communication and finding common ground are the keys to successful resolution. Focus on constructive ways forward.

7. Try to ameliorate concerns that can honestly be ameliorated

Give clear advice and honest professional opinions about the implications of delay. Delays in investigations are unhappily part of everyday experience in the NHS, and not always with as devastating implications as patients imagine.

8. Never criticise colleagues

Avoid comments that might incriminate colleagues. It would not help to focus on the fact that the respiratory team is largely away next week, as educational events are inevitable and essential components of medicine and you are not responsible for how another team has organised itself or at liberty to comment. Criticism of any colleague or department or service is always counterproductive. Most NHS employees are stretched and working together is paramount.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward

Assure him that you will find out exactly when his test is going to be.

Box 4.11 **Handling threatening, abusive and violent behaviour**

- Unhappily abuse by patients to staff is increasingly common, often threatening words but sometimes physical or even sexual.
- Doctors must avoid the temptation to take the law into their own hands, and first and foremost appreciate that there are often medical reasons for this (confusion due to infection or metabolic disturbance, for example) and such patients cannot be left without treatment.
- If threats are towards a particular staff member they should no longer be involved in that patient's care.
- Sedation may be considered if violence is a symptom of illness and it is necessary to prevent injury to patient or staff.
- Restraining measures are occasionally necessary, but may inflame or worsen a situation and cot-sides are frankly dangerous.
- Advice from a psychiatrist may be sought, especially if anti-psychotic medication is needed.
- Security should be called immediately if a patient is physically violent. But removal by the police is not acceptable if there are medical reasons underlying the behaviour.
- Empathy and practical support might need to be given to nursing and other staff.

Discussion

Would you encourage him to make a formal complaint?

He is perfectly at liberty to complain, but more imperative is to find a mutual way forward than potentially drive the divide further by encouraging a complaint. However, if he requests help in making a complaint you should direct him to the local complaints procedure. If you feel that there may be a system failure a Clinical Incident report could be forwarded to Trust Risk Management.

What do you do if a patient is threatening, abusive or violent?

Strategies are outlined in Box 4.11.

CASE 4.11 COMMUNICATING WITH UPSET OR DISTRESSED RELATIVES

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Mr George Tilner, aged 63 years

Ms Tilner is the sister of a 63-year-old man, Mr George Tilner, who has just died in the emergency department. He had advanced non-Hodgkin's lymphoma that was no longer responsive to chemotherapy, and had recently received palliative radiotherapy. He was admitted 2 hours earlier from a peripheral hospital with sepsis and peri-arrest but your rapid perusal of his case notes showed that he had spinal and renal metastases and you judge that a decision to resuscitate would not be appropriate if he had a cardiac or respiratory arrest despite fluids and antibiotics. He was an accountant and his last wish was that he completed his clients' work and that his briefcase be brought with him in the ambulance. You know that his sister is in the relative's room, and is very upset. Your personal feeling is that an advance decision should have been made to manage any deterioration at the peripheral hospital.

Your tasks are to explain to her that he has died, and manage the emotional situation.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the sister of Mr George Tilner, a 63-year-old man admitted to the emergency department 2 hours ago from a peripheral hospital. He has advanced non-Hodgkin's lymphoma that was no longer responsive to chemotherapy, and had recently received palliative radiotherapy. You have just arrived at the hospital, having received a call from nursing staff at the peripheral hospital to say your brother was very unwell with infection and was being transferred to the emergency department. He was an accountant and his last wish was that he completed his clients' work. Although you knew he was very unwell, you are still awaiting news from the doctor about his condition. You hope the doctors will do all that they can to save his life, but your sister-in-law is a district nurse and has gradually persuaded your over recent weeks that in the event of a deterioration from which recovery seems remote it might be best to 'let him go' peacefully. You are about to speak to the doctor.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

Introduce yourself and confirm the identity of the relative. Ideally, you would ensure that a member of the nursing staff is there, and talk in a setting where interruptions are very unlikely to occur. Sit at the same level as the relative, and use a calm tone.

2. Give vital information early

Do not give a detailed account of events up to his death, other than making it clear that he was very unwell.

> Ms Tilner, your brother was very unwell – comatose – when he arrived, and I am very sorry to tell you that he has passed away.

While bad news communicated to patients should be delivered gently with attention to cues from the patient, communicating the death of a patient to a relative should be equally gentle but not delayed, with attention to cues guiding subsequent discussion.

3. Deal with emotions before facts

She is unlikely to take in much more, if any, information immediately. Allow her time to exhibit emotions.

4. Acknowledge distress and support ventilation of feelings

Above all, people need to know that you understand, and you can do so non-verbally, practically (e.g. by offering tissues) or by acknowledging that emotions are understandable (legitimising). Remember that at this point patients are too preoccupied to assimilate further information.

5. Respond to patient cues

Throughout, be alert to any cues.

6. Gently explain what happened

Usually, distressed relatives say what they need to say, and you are there to support, acknowledge and provide whatever additional comfort seems intuitive.

> I know that he was very ill. And I know he wouldn't have wanted to suffer. His wife, my sister-in-law, knew that he didn't have very long. It's just such a shock. But he wouldn't have wanted things to drag on and be in pain, I know that.

It might be right to say, at this point:

> I know it may not be of any great comfort now, but I think it is important you know that I do not believe that he was in any pain … or even aware of things.

Keep all explanation clear and straightforward.

7. Do not raise personal concerns

Your feeling that acute admission might have been avoided with advance planning is not helpful at this time. Focus on supporting her through what has happened.

8. Identify patient support systems

Try to establish who, if anyone, is going to be available to be with her.

9. Check present information needs

While it is generally good practice to encourage feedback and invite questions, this is one situation where asking a relative if she has further questions can sound a little pressurising if handled as a direct question. It might be preferable to give an assurance that you can answer questions now but are available to talk further at any time later.

10. Make clear what support is available

> I'll leave you with sister/staff nurse for now, but I am here, and my team are here, at any time.

Discussion

How might you detach yourself from distressed relatives?

It can sometimes be difficult to detach yourself from relatives who are very distressed or upset, although largely there is a discernible point when all that is to be said has been said and relatives are not ready or able to ask more questions. You should always leave relatives with a point of contact, usually a nurse, and express your willingness to come back at any time if there is anything you might help with or answer.

CASE 4.12 DISCHARGE AGAINST MEDICAL ADVICE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Miss Sarah Walker, aged 23 years

Miss Walker was admitted 12 days ago with high fevers, subsequently confirmed as acute bacterial endocarditis. She has been on intravenous antibiotics four times daily with advice from microbiology. She was taking intravenous heroin until the date of admission and with assistance from the drug and alcohol advisory service is now on an appropriate methadone replacement regimen. She now wishes to discharge herself from hospital. She says that she feels better. She spends considerable time off the ward smoking, and the nursing staff have expressed concerns about possible ongoing drug misuse, as her partner meets her outside the hospital. Your medical plan is to keep her in hospital until her inflammatory markers are much improved, with repeat echocardiography. There remains the possibility of cardiothoracic surgery being needed if her valve decompensates.

Your tasks are to explore her reasons for wanting to self-discharge, discuss the medical reasons for her staying and find alternative solutions if she cannot be persuaded to stay.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Miss Sarah Walker is a 23-year-old woman admitted 12 days ago with high fevers, subsequently confirmed as acute bacterial endocarditis. She has been on intravenous antibiotics four times daily. She was taking intravenous heroin until the date of admission and with assistance from the drug and alcohol advisory service is now on a methadone replacement regimen but does not feel the dose adequate because she still feels psychological withdrawal. She is very keen to try to stop heroin altogether. She has two young children at home, both currently being looked after by her partner. She has little confidence in him doing so because he was the person who introduced her to drugs and continues to keep unreliable hours at home. She is meeting him regularly outside the hospital to try to negotiate his agreeing to her sister, whom she trusts, caring for the children. She now wishes to discharge herself from hospital because of her concerns. She spends considerable time off the ward smoking, but feels the attitudes of the nursing staff are prejudiced against this, while she feels it is currently her only enjoyment. Venous access is poor and although she has 'had enough' of treatment she might be persuaded to continue if she knows her children are safe.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Make it clear you want to help

It is crucial to start with the premise that she may have fully understandable reasons for wanting to leave hospital, and show that you are prepared to listen to these.

3. Explore concerns and reasons for wanting to self-discharge

Patients' stated reasons for wanting to self-discharge may mask deeper or more personal reasons. Fears for family members are often high on the list. Frequently a list of factors conspires to make the hospital unpalatable – uncomfortable investigations and treatments, poor communication, noisy wards, other patients, disturbed sleep, unpalatable food ….

4. Explain the medical reasons for wanting the patient to stay

This is essential for her to reach an informed decision because she might be unaware that the micro-organisms must be fully eradicated (and that this usually requires a few weeks of intravenous antibiotics) otherwise the problem will recur, with worsening damage to the valve. Explain also that the diseased valve must be reassessed after treatment. Confirm her knowledge that intravenous drug use is a high-risk practice for developing endocarditis.

5. Aim to address the patient's concerns

It would be wise to ask the social worker to review the welfare of the children. This could be presented in a non-judgemental way to her partner. He would have a right to look after his children if he is the father and he is fit to do so but if he is not the father, or if there are concerns as to his fitness to do so, then social workers could become involved on the presumption of assistance but in parallel explore the children's safety. It might also be possible for the children to visit hospital more or for her to be allowed home for periods of time between antibiotic treatment, although not wise to send her into the community with an intravenous cannula. Addressing her other concerns could also lessen the impact of hospitalisation.

6. Accept that the patient may self-discharge

It is, ultimately, a competent, informed patient's acceptable choice to self-discharge if she or he wishes.

7. If self-discharge seems inevitable, try to reach the best compromise

This might include discussing with the microbiologist the possibility of less frequent intravenous antibiotics delivered by a district nurse and/or oral antibiotics and early follow-up in clinic.

8. Confirm understanding and acceptance

Confirm that she is fully informed to make her decision.

9. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward and ensure follow-up arrangements are in place

Ensure that she signs a self-discharge form taking legal responsibility for her own care, document all discussions clearly and inform your consultant and her general practitioner of arrangements.

Discussion

Is a discharge against medical advice form a legal necessity?

It is not legally necessary, although it may enhance future evidence to obtain signed declaration by the patient that discharge is against advice. It is important to document that the patient had capacity and was fully informed and understood the medical reasons for staying.

CASE 4.13 DELAYED DISCHARGE

Candidate information

Role

You are a doctor on an elderly care ward.

Please read this summary.

Scenario

Re: Mrs Anna Clare, aged 93 years

Mrs Clare was admitted to your ward 1 month ago with numerous medical problems – inoperable peripheral arterial occlusive disease, anaemia due to aspirin-induced gastritis, dizziness induced by antihypertensives and back pain due to osteoporosis. She has a past history of recurrent strokes and may have had a further one whilst in hospital. She is now very unsteady even with a walking frame and assistance and unsafe to go home. She has poor memory. She accepts she may need nursing home care. Her daughter, Mrs Kenton, is keen on this but wants her to stay in hospital until the 'right one comes up.' An interim place is available in a home that is not the daughter's favoured choice.

Your task is to discuss potential discharge solutions with the daughter.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are Mrs Kenton, daughter of Mrs Anna Clare who is aged 93. Mrs Clare was admitted to hospital 2 weeks ago with numerous medical problems (previous strokes, poor memory, poor circulation, anaemia to aspirin, dizziness due to antihypertensives and osteoporosis). The major issue is that she is no longer safe from the point of view of either her mobility or her ability to be at home and has accepted long-term residential care. You have inspected numerous nursing homes on the advice of the social work department and have a very definite favourite where a bed will not be available for an indeterminate time, possibly many weeks. An interim bed is available and has been suggested by the discharge team in an alternative nursing home, but your father died in that nursing home and you do not want her to go there. You feel she would receive better care in hospital until the favoured placement becomes available, but would be amenable to considering alternatives that did not carry sad and emotive memories. You hope the doctor will agree to this and feel your mother deserves such care.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm the name/identity of the relative.

2. Make it clear that you want to help

Establish from the outset that you want to work with her to find the best possible solution that caters for the optimum care her mother deserves. The fastest way to dissolve rapport and thwart a way forward is to give the impression that you are there to tell her what to do.

3. Start by listening and agreeing

Ask her if she understands exactly what has happened to her mother during her lengthy hospital admission, and offer to summarise it. Then state ground where you are likely to both agree:

> That's right. We are, of course, very pleased that she has recovered somewhat from the problems that brought her into hospital. But there have been significant problems, as I know you are very much aware, some of which are unlikely to go away and some of which could even get worse over time. So it is the opinion of our nursing staff, our therapists, ourselves, and most importantly of course, herself and yourself, that she would be safer in the longer term in a place where full-time care could be provided.

4. Explore ideas, concerns and expectations

Explore any specific fears she has about particular nursing homes. There is a clear reason she does not want to proceed with one nursing home and that is very reasonable to accept.

> I understand. I am sorry that that one was suggested to you.

5. State a suggested management plan

> I understand that you have a favoured nursing home. We would of course support her getting a place there. What may be less easy is to get it quickly, and if that is the case then we need to think very carefully about finding a way forward that is acceptable to her and which provides for her needs.

She may say that hospital is surely the best place for her mother until such time.

> Hospital has certainly been the best place for her, whilst she has been so unwell. But an acute hospital setting is not necessarily the best place at this stage. Because our nursing staff and therapists are so necessarily occupied with their acutely unwell patients, they do not always have that much time with less acutely unwell patients, who by their very nature may be more stimulated to do things in a more streamlined setting. There are also risks to being in hospital that we often take for granted, but which should not be ignored – the fact that a hospital bed in a ward of acutely unwell patients carries by its very nature an increased risk of developing hospital-acquired infections.

6. Be alert to cues

She is likely to show acceptance or disappointment in your suggestions. Look out for cues, and respond if necessary.

7. Do not criticise hospital managers

Managers generally want to help and must give patients choice until the multidisciplinary team confirms the need for a specific transfer. Never tell patients or relatives you would like patients to stay in but managers will not allow it. We all have a duty to discharge or transfer as soon as appropriate. Managers are often prepared to come and talk with patients, explaining the number of acute coronary syndromes waiting in emergency departments (there has been an appreciable increase in medical admissions since the mid-1990s but an unparalleled and relentless sharp upstroke, especially in the elderly, since autumn 2004 – with complex reasons but perhaps in part related to a decrease in out-of-hours primary care) and assuring patients that they will get the bed they want but that they cannot wait for it in an acute hospital bed. What they cannot do is put a patient in an exiting ambulance against their will (assault) or evict (not legally tested and brave the Trust that tries!). There will always be the difficult or resistant 1% of patients or relatives (but with the best of intentions and at an emotional time).

8. Encourage feedback and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

9. Confirm understanding and acceptance

Make sure that she is generally accepting of your suggestions so far.

10. Agree a way forward

Agree, for example, to speak to the hospital discharge team and discuss appropriate interim alternatives.

Discussion

What is an integrated care pathway (ICP)?

ICPs aim to map a patient's journey from admission to discharge or beyond and have been used for many conditions including stroke but have not been shown to improve outcome measures where a unit already functions well. ICPs are more useful in setting up a new unit from scratch. Clerking proformas for particular diseases such as stroke, however, may be useful.

Hospital trust managers are very keen on discharge planning. Do you think you should be as concerned as your hospital managers?

Discharge planning is a crucial part of modern hospital practice, and often badly managed. Depending upon the patient, it might include information to patients and carers, training of carers, pre-discharge home visits by the multidisciplinary team (initially to assess the home and subsequently to assess the patient in their home), pre-discharge case conferences for patients with complex care packages, clear instructions of who to contact should there be problems, further community rehabilitation at home or in a day hospital and follow-up arrangements.

What is early supported discharge?

Early discharge of selected patients is cost effective and safe (shown by Langhorne and colleagues in a metaanalysis published in the *Lancet* in 2005). It might include three to seven daily visits per week for up to a month by the multidisciplinary team (e.g. occupational therapy assistant, physiotherapy assistant, health-care assistant).

Is there a role for discharge teams?

Increasing pressure on ward staff with acute admissions within a target-driven health service, and in the context of changing community resources and a thrust towards patient choice, has led to difficulties in finding time for optimum discharge planning. Discharge teams assist when complex discharge is likely. Such patients might be elderly, need rehabilitation, have social problems including homelessness, or have palliative care needs. Concerns might also be raised by the family. Discharge teams help patients through the system by ensuring maximum utilisation of community hospital beds, identifying rehabilitation needs, ensuring timely paperwork, working with, for example, social work and palliative care, and generally acting as a resource for discharge-related dilemmas. Patients will generally be discharged to one of three settings, as follows.

Home

A good social history is vital, and discharge teams may work to integrate this information, for example by using a booklet at the end of the bed for the patient and family to fill out, along with:

- Assessing the realism of the patient's expectations
- Ensuring early referral to occupational therapy, physiotherapy or social work
- Prompting multidisciplinary discussion
- Prompting specialist assessment of care needs (SACN) and care packages

- Identifying community resources such as nurse specialists, the voluntary sector, the housing department and interim placement.

Rehabilitation or other interim settings

Discharge teams coordinate rehabilitation or other community beds for patients who might benefit from rehabilitation or for patients with chronic diseases, who have palliative care needs or who are awaiting care packages or assessment for entry into long-term care.

Care home (residential or nursing, but the term care home has been adopted since 2003)

Ideally the patient, family and the multidisciplinary team should agree on this. Once medically ready for discharge and the SACN has been given to the social work department, a patient's discharge is officially delayed, and there then arises:

- Pressure on the patient and family to find a care home (or accept interim placement) based on advice from social workers as to which may be appropriate based on the SACN (if a nursing home is needed then the nursing home staff also assess the patient)
- Pressure on the social work department, whose reimbursement starts dwindling for each day lost, and pressure on the hospital because an acute bed is blocked.

What is meant by delayed transfer of care (DTOC)?

DTOC occurs when a patient is ready for discharge from an acute bed (clinical decision, multidisciplinary team decision, safe to do so) and there is no medical reason for the delay. There are various categories, depending on the reason for DTOC, such as lack of availability of onward placement, delayed funding, delay in arranging domiciliary packages or delay in community equipment. It incurs bills immediately to social services. The conflicting mantras imposed on the NHS of expanding patient choice (which often drives unrealistic expectations) and targets for acute care (with 4-hour movement through emergency departments but prompt discharge if there is not an acute problem) mean that doctors and managers must work together towards the same goal.

What is meant by the term intermediate care?

This refers to care outside the acute setting that occupies a transition period to another setting. It includes rehabilitation after an acute event, responses to an overt crisis and care whilst long-term care is being considered or assessed.

How is a patient assessed for entry into long-term care?

Individual trusts have developed processes assessing not just the medical diagnosis and treatment but multidisciplinary team assessment of breathing, feeding and diet, gut function, bladder, toileting, dressing, mobility and transfer, stair assessment, skin, pain, sensation (hearing, vision), communication, comprehension, sleep, memory, depression and anxiety, initiative and involvement, relationships, past roles and physical behaviours. Also considered are requirements for equipment.

What is meant by the term continuing care?

This refers to a situation where, following a thorough assessment of needs, a person's overall health needs are judged to be so great that the NHS will manage and pay for all the care they need. An NHS professional supervises the agreed care plan, which can be in any setting, for example a person's own home, a hospice, care home or hospital.

Breaking bad news

CASE 4.14 CANCER – POTENTIALLY CURABLE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr James Oakley, aged 58 years

Mr Oakley is a previously well man on your ward with recent night sweats, weight loss and abdominal discomfort. He works as an information technology consultant and has been under a lot of work stress recently, travelling a lot and under pressure to meet sales targets. He attributed his symptoms to this but his general practitioner admitted him with high fever and marked splenomegaly. He was initially treated for possible atypical pneumonia but his full blood picture suggests possible chronic myeloid leukaemia. The haematology team plan to perform a bone marrow aspirate and trephine but he wants to know the diagnosis you suspect.

Your task is to discuss the possible diagnosis, addressing his concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr James Oakley is a previously well 58-year-old man with a history of recent night sweats and abdominal discomfort. He works as an information technology consultant and has been under a lot of work stress recently, travelling a lot and under pressure to meet sales targets. He attributed his symptoms to this but his general practitioner (GP) admitted him with high fever and marked splenomegaly. He was initially treated for pneumonia but his blood tests are apparently not so straightforward. The haematology doctors plan to perform a bone marrow aspiration but he wants to know why, and what diagnosis his doctors suspect. He is married with two children and is keen to get back to work soon.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

'Bad news' is any information that drastically changes a patient's view of their future for the worse. The way in which it is communicated affects their perception of the situation and, crucially, their attitude to living with an illness and the ability to adjust. Many candidates are naturally adept at creating rapport and building a feeling of trust with patients. Important components of preparing include:

- Having the time and privacy to talk without interruptions
- Being clear about the diagnosis, problem or test results so far and suitable ways forward
- The presence (not in PACES) of a supportive co-worker such as a named nurse or ward sister
- The presence (not in PACES) of a relative or close person if a patient wishes
- Sitting close enough for good eye contact and detection of non-verbal cues; sitting at the same level as the patient rather than above (or worse, standing) is less threatening to an already apprehensive patient
- Opening with a neutral statement:

  How are you feeling today?

  You and I know that you have had these pains in your tummy for some time now.
- Active listening, being attentive to what you hear and showing concern and empathy through eye contact, head nodding and other natural body language.

In short, your patient should feel that this discussion is the most important thing on your agenda, and not that you are distracted.

2. Establish what the patient knows already

Establishing previous experience and knowledge is crucial. The rule is to ask before telling with such questions as:

Can you tell me what you understand about your illness?

What have you been told about things so far?

I believe you put your symptoms down to stresses at work. Did any other possibilities cross your mind?

Have you thought about any other possibilities for the cause of your symptoms?

Such a question both explores ideas and concerns and prepares for more serious news. He might elaborate his concerns about the possibilities. Non-verbal skills such as silence, active listening and simple words such as *yes*, *and then* and *hmm*, and repeating and reflecting back information you are told can be very effective.

So you had been worried about something like that?

He might indicate immediately that he has an idea of what might be wrong:

I'm worried it might be cancer.

If he already suspects a diagnosis then it is possible to gently confirm rather than break bad news at this stage.

3. Establish what the patient wants to know

A very useful step if handled well. Possible questions are:

You said you wanted me to be honest and open with you. Are you the sort of person who likes to know everything about his condition?

Would you like me to explain the problem as we understand it so far?

We can't be certain of what is wrong from the tests so far. But are you the sort of person who likes to know all the possibilities?

How much information would you like me to give you about your diagnosis and treatment?

Patients tend to declare outright or indicate that they do not want to talk about their disease (in which case it may be appropriate to ask if they would like you to explain things in more detail to a relative) or they want to know more.

4. Give a warning shot

When a patient is apparently unaware of potential bad news, the skill is in conveying information without provoking overwhelming distress or pushing them into denial:

I'm afraid that things look a little more complicated than we had thought/hoped.

I'm afraid it doesn't look like a straightforward infection.

The next thing to do is wait! Allow time for the warning shot to sink in. He can signal that no further information is wanted:

Just tell me what we have to do next.

or that more information is wanted:

What do you mean not straightforward?

5. *Break bad news gently*

> When the pathologist looked at the blood samples he found some abnormal cells.

Again, he can signal 'enough':

> What do you need to do next?

or 'go on':

> What do you mean by abnormal? I need to know if you mean what I think you do?

At this point be as honest and informative as possible:

> There is a possibility that they might be cancerous, a form of blood cancer or leukaemia.

Bad news should always be broken gently but not be unduly delayed. It should be given in clear, simple, small pieces and patients should be given plenty of opportunity to respond or question at any stage. Important information should be repeated and patient understanding might need to be checked, remembering that patients are likely to experience a heavy impact and that repeating the word 'cancer' is not necessary unless it is very clear that it has not been understood. Such fear words are best used only when a diagnosis is established beyond doubt or is a strong possibility.

6. *Acknowledge distress and support ventilation of feelings*

Above all, people need to know that you understand, not that you feel sorry for them. You can do this non-verbally, practically (e.g. by offering tissues) or by acknowledging that emotions are understandable (legitimising):

> It's normal to be upset. I understand that this is very hard.

Never rush in with immediate optimism or reassurance *(I'm sorry to tell you it's cancer but the good news is/let me tell you what we can do . . .)*. Always remember that at this point patients are too preoccupied to assimilate further information. Research shows that subduing or not allowing ventilation of feelings and concerns thwarts recall of what you tell patients next.

7. *Identify and prioritise concerns*

It may be appropriate, after a while, to ask:

> What are the particular things you are thinking about?
>
> How does this news make you feel?

It is always important to elicit all concerns before giving advice or information. When concerns are not explored or patient needs not established patients are more likely to remain preoccupied with their concerns, fail to assimilate what is said, perceive information as inadequate and develop anxiety or depression that will hinder the control of future symptoms such as pain.

8. *Check present information needs*

> Is there anything else you want to ask me about?
> Do you want to tell me anything more?

Research shows that too much information can cause as big a problem as too little.

9. *Identify patient support systems*

> Who is at home with you?
>
> What about family/friends/others?

10. *Make clear what support is available and what is going to happen*

Never remove all hope, however bad a diagnosis, giving absolute assurance of what can be done and what should be done next – further investigations or treatments, support of hospital staff, GP, nursing staff, support groups and so forth and follow-up arrangements (making it clear that the patient can be seen at any time before this if there are questions or concerns).

Discussion

How should bad news be broken?

There are many suggested approaches on how best to break bad news. The truth is that there are many acceptable ways to do it, and many unacceptable ways. One guide or framework for breaking bad news is to use the SPIKES acronym:

- **S**etting: Point 1 above
- **P**erception: Point 2 above
- **I**nvitation: Point 3 above
- **K**nowledge: Points 4 and 5 above
- **E**mpathy: Points 6–8 above
- **S**trategy and summary: Points 7–10 above.

Box 4.12 **Mistakes when breaking bad news**

- Avoiding it in the first place and expecting that someone else will do it
- Not scene setting appropriately, e.g. not enough time or not in privacy
- Not establishing background knowledge
- Not establishing how much the patient wants to know
- Giving the bad news too quickly, rather than gently
- Hesitating too long before getting to the bad news, e.g. a junior emergency department doctor goes to speak to anxious parents about the accident their child has had; the doctor explains what happened in detail, what was done in the resuscitation area and only after considerable time tells them that the outcome of their efforts to resuscitate was unsuccessful
- Not acknowledging the patient's distress
- Not exploring the patient's concerns
- Not exploring the patient's information needs
- Being dishonest, e.g. 'We think you'll be all right.'

Of course no single formula guarantees effective and sensitive delivery of bad news, but appreciation that it is a conversation in which each exchange directs the next step – based on evolving knowledge and feedback and your own intuition – is key. This is why the more experienced, senior members of the team should ideally break bad news.

Can you think of some common mistakes when breaking bad news?

These are listed in Box 4.12.

CASE 4.15 CANCER – PROBABLY INCURABLE

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Please read this summary.

Scenario

> Re: Mrs Jean Paget, aged 86 years
>
> Mrs Paget is a previously well woman with mild hearing difficulty, in clinic for the results of recent investigations for iron deficiency anaemia. She was discharged from hospital 3 weeks ago following a transfusion to correct her anaemia. Subsequent urgent outpatient investigations comprised an oesophagogastroduodenoscopy (OGD) and an abdominal computed tomography (CT) scan. Colonoscopy was not performed, jointly agreed by patient and doctor on account of her being physically frail and it being against her wishes. The OGD showed an isolated, large gastric ulcer for which she has started a proton pump inhibitor and preliminary histology confirms malignancy but not the type. The CT scan shows two large cystic masses in the pelvis, probably arising from an ovary. The radiology report suggests that these may be malignant, but you have not had an opportunity to discuss the scan in any more detail with the radiologist. Mrs Paget's daughter and son-in-law are present, supportive family members with whom Mrs Paget lives.
>
> Your task is to break the news to Mrs Paget.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Jean Paget is an 86-year-old woman who lives with her daughter and son-in-law, supportive family members accompanying her in clinic today. She has come for results of outpatient tests. She was discharged from hospital 3 weeks ago following a transfusion to correct anaemia. The urgent outpatient tests were performed to look for a reason for anaemia and were upper gastrointestinal endoscopy and an abdominal computed tomography (CT) scan. Colonoscopy was not performed, jointly agreed by her and the doctor when in hospital on account of her frailty and it being against her wishes. Mrs Paget has mild hearing difficulty but has previously been well and is not taking any regular medications. Cognition is normal but she is functionally limited by arthritis and dependent on her family to assist her with dressing and meals. She has not really considered possible diagnoses but feels that 'at her time of life' she can accept any bad news.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

Introduce yourself, ensuring that she can hear all that is said. You may need to speak up. Ensure that she and her family do not sense that you are pressured for time. Sit forward, remembering that your first duty is to her, aiming for good eye contact and active listening. Ask if she agrees to your speaking openly with her and her family:

> May I take it that you are happy for us to speak openly in front of your family?

2. Establish what the patient knows already

At this point, it is appropriate to seek her knowledge of the reasons for investigation so far:

> Could I ask, first of all, what you understand about the reasons for your recent tests?

It may be helpful to summarise:

> You will recall that we recently found you to be anaemic – your blood count to be low – and that one of our concerns was that there might be a reason for this in the tummy, giving rise to a slow leakage of blood internally. That is why we agreed we have a look into the tummy with the endoscopy, together with a scan.

3. Establish what the patient wants to know

The rule is to ask before telling, but not to delay breaking bad news. In this situation it may be appropriate to say:

> We have the preliminary results of those tests, and I take it you would want me to be frank with you about everything that we know.

4. Give a warning shot

> There was an ulcer in the stomach … and, in addition, two lumps in the pelvis were seen on the scan … and the early signs are that these findings may not be nice.

Wait for a few seconds for this to register!

5. Break bad news gently

The key here is to continue explaining results clearly and slowly, taking account of her reaction as each piece of information is related:

> The biopsy – when they took a small piece of tissue from the stomach – suggests that the problem may be a growth.

6. Acknowledge distress and support ventilation of feelings

At this point there may be little value and further distress in giving more details unless she asks for more information. Now respond to reactions with appropriate gestures (it may be reasonable to touch on the forearm, for example, during the above explanation).

7. Identify and prioritise concerns

Be open to any questions that she or her family might have.

8. Check present information needs

At the end of this, she might ask what needs to be done. You do not have enough information to suggest a definite course of action, but you can hypothesise:

> We are still waiting for the final pieces of information from the biopsy. And I would also like to see the pictures of the scan myself and discuss these in more detail with the radiologist. But if this is what we suspect, then you and I will need to discuss the way forward. It seems likely that the lumps in the pelvis are connected to what we have found in the stomach, but even if they are not, then I do not think it likely that an operation on the stomach would be the answer. An operation is, I think, unlikely to be possible and even if it were, it would not be without considerable risk. There is a possibility that we might hold things at bay for a period of time with some other form of treatment – drug treatment. But the other consideration that would be for you and your family to think about is that, if you are having no symptoms, it may be reasonable to leave things alone.

She might then ask:

> And what would happen then, doctor?

You would need to make it very clear that you would have a plan to support her:

> We would talk with your doctor (general practitioner) and let him/her know of the situation in full, so that treatment can be given for any symptoms that arise. But in the first place, I think it would be sensible for us to meet again in a week or so, by which time we should have the final results of the biopsy and I should have had an opportunity to review your scan in more detail with the radiologist.

In other words, it is often desirable to discuss the diagnosis of cancer at the first appointment, but defer any definite decisions about the way forward (especially if results are still pending) until a second appointment (or subsequent ward round for inpatients), by which time patient and family will have had time to discuss the implications amongst themselves.

9. Identify patient support systems

Find out a little about how things are at home.

10. Make clear what support is available and what is going to happen

Agree to meet again in the very near future to consider the best way forward.

Discussion

What information would you need before seeing her again?

A review of the CT scan with the radiologist, the final histology report and possibly a CA125 blood test.

The radiologist, at a second view, thinks the pelvic masses could be simple cysts and are likely to be unrelated to the gastric malignancy. The histopathology of the latter, surprisingly, reports a high-grade non-Hodgkin's B-cell lymphoma rather than carcinoma. When you see her again, will you attempt to persuade her to have treatment?

You would, of course, discuss the results and reach a shared management plan. You might suggest that the only way to be sure about the pelvic lumps would be to obtain a biopsy, and this would require further hospital intervention. But that this does not escape the fact that there is, involving the stomach, a form of growth called lymphoma that is not treatable by operation. There may be a possibility of treatment involving chemotherapy or radiotherapy, but to know the absolute answer to this one would need to obtain more information and seek advice from a specialist who treats lymphoma.

She asks if she will die without treatment. How might you respond?

It is sometimes worth exploring why patients ask this question. It might seem obvious, but it is important to know what patients are thinking and saying:

> I can answer that. But could I firstly ask you why you've asked me that?

might help you understand her main concerns or fears. She might tell you that her husband had chemotherapy and that she does not want any treatment if it is not going to make her better or cure her and ask:

> Could we do anything else, doctor?

to which you could tell her:

> We could make sure you were as comfortable as possible and try to let you spend as much time as possible at home.

She says that she does not wish more hospital tests or treatments. She says 'When my time has come, my time has come; I'd rather take my chances than have any more tests or treatment.' Would you accept this?

If this is her informed choice, yes.

CASE 4.16 CANCER – PATIENT NOT FIT FOR ACTIVE TREATMENT

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Rose Broadley, aged 79 years

Mrs Broadley has been under your team's care for almost a week, and is receiving anticoagulation for two large pulmonary emboli diagnosed on admission. She has been non-specifically unwell for the past 2 months, feeling tired and losing a little weight and admission to hospital was arranged when she developed worsening breathlessness. Unfortunately, she also has a swollen left thigh and groin with an ulcerated patch from which meticillin-resistant *Staphylococcus aureus* has been cultured and is receiving intravenous antimicrobials. Inflammatory markers have been high, perhaps not surprisingly, but because of the systemic symptoms and the absence of any clear precipitating cause for her pulmonary emboli, a computed tomography scan of thorax, abdomen and pelvis was arranged that revealed a large caecal mass and para-aortic lymphadenopathy. The diagnosis is almost certainly cancer. Mrs Broadley asked earlier in the week if the reason for the scan was to look for cancer, which you confirmed.

Your task is to explain results, and discuss possible ways forward.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Rose Broadley is a 79-year-old woman who has been in hospital for almost a week, and is receiving anticoagulation for two large pulmonary emboli diagnosed on admission. She has been tired and losing weight for 2 months and was admitted to hospital when she developed worsening breathlessness. Unfortunately, she also has a swollen left thigh and groin with ulceration from which meticillin-resistant *Staphylococcus aureus* has been cultured and is receiving intravenous antibiotics. Her doctors were concerned as to why she developed pulmonary emboli and a computed tomography scan of her thorax, abdomen and pelvis was arranged. Mrs Broadley is a pragmatic woman who likes to know the facts, is aware that there is a suspicious lump that can be felt in her abdomen and that the scan was to look for evidence of cancer. She is about to speak to the doctor who has the results.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

This case combines confirming bad news to a patient who already knows it is a possibility with making a management plan. The problems are complex, and the discussion should focus on possibilities rather than making absolute decisions now. In real life discussion might be with her alone or with relatives if that is her wish, and ideally in the presence of her nurse. It seems very likely she has colorectal cancer with lymph node spread and that this explains her thromboembolic tendency. The challenge is that you do not have a tissue diagnosis, and the need for anticoagulation and the sepsis make further investigation (colonoscopy, biopsy) and potential treatments (curative surgery or surgery to debulk tumour and reduce the likelihood of obstruction and/or chemotherapy) difficult. These facts need to be included in your discussion.

2. Establish what the patient knows already

You know that she understands what has been happening, but it is still helpful to summarise:

> As you know, it has been a difficult sequence of events. You have been feeling unwell for some time, and when you first came into hospital we suspected, and confirmed, a blood clot on the lung. This was compounded, as I know you are all too well aware, by the infection in the upper part of the leg. And you know, as we have discussed, that we were rather worried that there might be some underlying reason for all of this happening to you … hence, the scan.

She will probably acknowledge all of this. Whilst vital not to delay giving the results of the scan, a preamble like this not only leads seamlessly into breaking the bad news but also shows that you are fully aware of her case and this is crucial to maintaining her confidence.

3. Establish what the patient wants to know

Here you may assume that she wants to know everything.

4. Give a warning shot

> The scan does give us a reason for all of this. It does show an abnormality, and one that may not be nice.

5. Break bad news gently

It shows a lump, within the bowel – within the lower part of the bowel – that is of considerable size.

She will probably register understanding. It may be appropriate to confirm, as patients cannot start to ventilate feelings until you do:

It is very likely to be a growth.

Occasionally, if you choose to use the word growth rather than cancer, patients will rephrase this by asking *Cancer?* – to which it is appropriate to confirm that single word. It may then be appropriate to say that there are also lumps in glands adjacent to the bowel.

6. Acknowledge distress and support ventilation of feelings

Now give her time to come to terms with this news.

7. Identify and prioritise concerns

As a pragmatic woman who has already suspected serious possibilities, she will probably want to know what needs to be done. The following is an outline of areas your discussion should explore. Speak clearly and not too quickly and be ready to address questions or clarify information throughout.

There are a number of things to consider. The first is that, although it seems very likely that this is what we suspect it is, the way to be certain would be too look directly into the bowel with a flexible telescope with a light on the end – a test called colonoscopy – and that would enable us to take a needle sample from it.

The problem is that the blood-thinning medication you are taking makes it a little tricky, though by no means impossible.

We strongly suspect that the colonoscopy would show a growth, and a nasty one. The reason that we would do it would be to consider what to do about it, including surgery or other forms of treatment.

I would suggest that we do not make any decisions now but simply say that ultimately we have to decide – and in the last analysis you have to decide – what is the right thing to do.

8. Check present information needs

She might want to know more about possible treatments:

We might be in a position to consider an operation. And what we would like to do, if you agree, is to ask one of our specialist surgical doctors to see you and talk though what they think possible. An operation would not be without considerable risk, because of the blood clots and because of the infection, and because of the infection it is not something we could consider immediately.

An operation, depending upon what was found, might carry a possibility of getting rid of it, but also the possibility of not getting rid of it completely. On the other hand, you might decide that, even if surgery were possible, you would not wish it. And simply accept that things are likely to progress.

We would fully understand if you were to say 'if you're not sure it's going to make it go away, I don't want to go through the pain of an operation'. On the other hand, if you were to say 'I know it's risky but if it's the only way to possibly make things go away…' we would do our best to bring everything, and everyone, together to make that happen.

One thing that you should be aware of is that, if surgery cannot remove it completely, it might be possible to remove some of it and that without surgery there is a possibility that things could, at some stage, become obstructed.

We will respect whatever you decide/We will do our best whatever you decide. It's not an easy decision to make, I know.

She may want to know what would happen without further treatment.

We would simply keep a very close eye on things, and do whatever we can to ease/alleviate the situation.

9. Identify patient support systems

Find out a little more, if you do not already know, about her home circumstances.

10. Make clear what support is available and what is going to happen

What I would suggest, if I may, is that we think about this a little more and talk again. Meantime, if you agree, we will ask the surgeon to give an opinion on surgery. And we are here at any time, before we next meet, if there is anything you want to discuss, or if you would wish us to sit down with you and your family … I am here, other members of my team are here, and ward sister is here.

Discussion

An elderly woman has liver metastases from an unknown primary site. She is frail, deemed medically unfit to undergo more than palliative treatment, and wishes to know 'just what I need to know, doctor, but no more'. You judge her mental capacity to be borderline. What might you tell her?

She could be told that the news is not good; that there is trouble in the liver that is not nice (to use the word growth or cancer would very much depend upon feedback from her); that a lot of tests could be done to try to find out where it came from, but that there would not seem to be any ground gained by subjecting her to uncomfortable tests; that the fact is the growth is here, and that it seems best now to try to get her home, perhaps with a period of convalescence, with the support of family, and keep a close eye on things, treating any symptoms such as pain if and when they arise.

An 88-year-old man has been losing weight. He smokes and has a recent Horner's syndrome and a Pancoast's tumour clinically. He was informed that this is worrying. The chest X-ray now confirms it. What would you tell him?

Using the 10-step framework for breaking bad news, he might be told:

> Remember how we discussed that we were very worried about things. The X-ray confirms our worries. What we are seeing may not be nice.

If he does not indicate that he has heard enough:

> We must wait until we know exactly what we are dealing with, but there is a high possibility of a growth.

When he is ready, he will want direction, but may not know what to say. He may say something as open ended as:

> Not good, is it?

You must not leave him without support and clear sense of your ownership in helping him:

> No, but it is here. And what we must now do is decide how we are going to deal with what is here.

CASE 4.17 CHRONIC DISEASE

Candidate information

Role

You are a doctor in the neurology clinic.

Please read this summary.

Scenario

Re: Mrs Amy March, aged 28 years

Mrs March was referred to the neurology clinic 2 months ago with blurred vision in her right eye, subsequently diagnosed as a second episode of optic neuritis; she had had a similar episode 6 months previously and attended the eye clinic. During her last visit, it was suggested by the neurologist, when she asked, that her symptoms could be due to multiple sclerosis. Magnetic resonance imaging arranged after that appointment and performed last week has been reported as showing multiple demyelinating plaques in the brainstem and periventricular areas consistent with multiple sclerosis.

Your task is to explain the diagnosis.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Amy March is a 28-year-old teacher who presented to the eye clinic 6 months ago with blurred vision in her right eye, diagnosed as optic neuritis. A second episode occurred 2 months ago and she was referred to the neurology clinic where it was suggested to her, when she asked, that multiple sclerosis was a possibility. She is at the clinic today for results of a magnetic resonance (MR) scan to look for evidence of multiple sclerosis. She is very concerned about what a diagnosis of multiple sclerosis might mean if she wished to become pregnant, and the future implications of this disease.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

Introduce yourself, and ask how she has been since the last appointment.

2. Establish what the patient knows already

Establishing previous experience and knowledge is crucial, not least exactly what she was told about the possibility of multiple sclerosis and whether she had still been thinking about it.

3. Establish what the patient wants to know

Establish what has gone through her mind about multiple sclerosis, and if it engendered any particular worries. Here you may assume that she wants to know everything.

4. Give a warning shot

Tell her that the scan does confirm the thoughts that the neurologist had last time.

5. Break bad news gently

Explain the results of the MR scan, that it does suggest multiple sclerosis and allow her time to take this on board.

6. Acknowledge distress and support ventilation of feelings

Watch for her reactions.

7. Identify and prioritise concerns

When she appears ready, explore particular concerns. Tell her that people with multiple sclerosis can have very healthy pregnancies, indeed that sometimes multiple sclerosis tends to improve during pregnancy, although symptoms can flare up after delivery and so close monitoring is needed from the obstetrician and neurologist. Reassure her that not all patients develop disabling disease, and that it can vary very much from one patient to another but that most patients continue to lead normal lives. Explain that it tends to relapse and remit, but that some patients go for many years between relapses. Explain that her specialist will discuss what, if any, treatments might be desirable at this stage.

8. Check present information needs

Do no overwhelm her with information; at this stage, largely respond to her concerns:

> Is there anything else you want to ask me about?
>
> Do you want to tell me anything more?

9. Identify patient support systems

Establish who is at home with her and if her symptoms have interfered with her work at all.

10. Make clear what support is available and what is going to happen

Explain that you will speak with the neurology consultant about any treatment and ensure that things are kept under review.

Discussion

Would you allow a patient in denial of their illness to continue in such denial, or attempt to change this?

Occasionally, it is necessary to challenge denial because it hinders their ability to deal with important unfinished business or their treatment. It is sometimes possible to confront patients gently by highlighting the inconsistencies, such as a declared belief they are getting better in the face of increasing disability. But where a patient is in persistent denial, it may be because they are unable to tolerate the pain of reality and leaving them in that defence mode until further opportunities during the illness may be best.

CASE 4.18 DISCUSSING AN ACUTELY TERMINAL SITUATION WITH RELATIVES

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Mr Frank Wentworth, aged 88 years

Mr Wentworth is an 88-year-old man admitted to hospital 2 hours ago with a thoracic aneurysm rupture ('mediastinal catastrophe') diagnosed clinically and with a radiologically wide mediastinum on chest X-ray. You wondered about a computed tomography scan but your consultant feels that the diagnosis is beyond significant doubt, that there is no alternative, reversible explanation for his presentation and that a scan would not alter management. A team decision has been reached to keep him comfortable. You have just come back to review him, and his daughter is now with him. You have not spoken with her before but it is clear to her that her father is very unwell and it appears to you that he is deteriorating quickly because he is less alert than 2 hours ago, with gradually falling blood pressure. You offer to go to the ward sister's office to discuss her father's case.

Your task is to discuss with her what has happened and what the outcome is likely to be, responding to her distress.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the daughter of Mr Frank Wentworth, an 88-year-old man admitted to hospital 2 hours ago with a ruptured thoracic aneurysm. You are a schoolteacher, phoned at work by a nurse at the hospital to say that your father was very unwell and that you should come in. You have just arrived. You do not know anything else, but have been at the bedside for a few minutes and can see that your father is clearly critically unwell and barely conscious. You are not really sure what an aneurysm is but fear the worst, although you do not think this means imminent decline. Your husband is also on the way to hospital. Your father has previously been very healthy, playing golf until last year. He has been widowed for 2 years but has remained independent on his own. You have been invited to the ward sister's office to talk to the doctor. You are extremely worried and will be very distressed to hear the worst but need to know exactly what the doctor thinks.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Preparation and scene setting

Introduce yourself, and sit close enough to allow good eye contact and at her level.

2. Establish what the relative knows already

Ask what she knows so far but do not labour it; she will want to know what is going on straight away.

3. Establish what the relative wants to know

This step in the breaking bad news 10-step sequence should be bypassed if it is clear that she is waiting in distressed anticipation of what she needs to know.

4. Give a warning shot

Simply saying:

> (I'm afraid) the news is not good

may be enough to start.

5. Break bad news gently

Explain what has happened, clearly and calmly. So that there is little doubt of the critical position, one way to conclude the explanation would be to say:

> There may not be an easy way out of this … there may not **be** a way out of this.

pausing between both statements, the first telling her gently that he may not recover, the second building on the first to inform her that you may have run out of options to save his life.

6. Acknowledge distress and support ventilation of feelings

She will be very distressed and now is the time to let your comments sink in, and not the time to give more information.

7. Identify and prioritise concerns

Every case must be treated on its own merit. Sometimes it is appropriate to ask how a patient feels about bad news that has been broken. Here, it would be inappropriate to question her thoughts, which are obvious, and you should simply continue to acknowledge her distress, respond to questions and speak honestly, clearly and with understanding.

She may ask:

> What can you do?

A suitable reply would be:

> We can only watch and wait and see if the bleeding stops. It is all that we can do. There is simply no way of getting to where the bleeding is. He may be dying.
>
> Right now?
>
> Yes.

It can be difficult for relatives to accept such abrupt news like this. But it is vital to be straightforward and honest.

> Things are absolutely critical.

8. Check present information needs

> How long do you think he has got?
>
> These hours are critical.

One concern that it is always helpful to anticipate and mention is about pain and distress.

> What we can do is make certain that, whatever else, he is not in any pain or distress. As he becomes less conscious it is very unlikely he will feel any pain, not at this stage. But if we had any reason to suspect discomfort at any stage we could treat that with medication, with morphia.

9. Identify support systems

You may wish to check that her husband is on his way, and whether or not she has other relatives who should be aware of the situation.

10. Make clear what support is available and what is going to happen

Assure her that the doctors and nursing staff are available at any time to speak to her again.

Discussion

Patients with incurable but more chronic conditions often ask about how much time is left. How might you respond?

Clearly it depends upon the situation. It is important to acknowledge that you cannot be certain but patients then often ask you to guess. It may be appropriate, if realistic, to say something such as 'Well, the way things have been going it might be just months', but while it is important to be as honest as possible about prognosis it is important not to give specific time frames. Patients sometimes ask about specific dates like whether they will be here for Christmas. You might say 'I would hope so', but ask if there is any reason they mention Christmas in particular. It might be, for example, that a relative died at Christmas and the patient is worried that it will be particularly hard on other family members.

Why is it important to respond to questions about prognosis?

Patients might otherwise be misled about their outlook and might not use their remaining time to deal with important practical and emotional unfinished business with loved ones. This will also make the bereavement process more difficult for loved ones and increase psychiatric morbidity from, for example, major depressive disorder.

Confidentiality, consent and capacity

CASE 4.19 LEGAL POINTS IN CONFIDENTIALITY

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Marcia Smith, aged 30 years

Mrs Smith, a Thai woman who speaks good English, was admitted to the ward with abdominal discomfort and fatigue, now confirmed to be due to hepatitis B infection. She also has inguinal lymphadenopathy and you have sought her consent for a human immunodeficiency virus test. She has lived in the UK for 6 months with her English husband whom she met and married a year ago. She refuses the test. She also tells you not to tell her husband her diagnosis.

Your tasks are to explore her reasoning, and discuss the importance of the test and possible consequences of refusal.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Marcia Smith, a 30-year-old Thai woman who speaks good English, was recently admitted to hospital with abdominal discomfort and fatigue, now confirmed to be due to hepatitis B infection. She also has lymph node enlargement in her groin and her doctors have asked if she might consent to a test for human immunodeficiency virus (HIV). She has lived in the UK for 6 months with her English husband, whom she met and married a year ago. She is very afraid. A friend of hers died 2 years ago from HIV in Thailand, although sustained treatment had not been available. She is also very afraid for her 2-month-old baby, and her husband. She does not want the doctors to perform the test, nor tell her husband of her current diagnosis.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Establish rapport

There is potential conflict between her right to confidentiality and the rights of her husband (and baby) to information and possible treatment in the event that he (they) was (were) infected. From the outset, you may be balancing her confidentiality against potential risks to others. But avoid giving her 'ultimatums' at this stage. It is vital not to 'rush in'. Your first duty is to her, analysing her perspective and how you may best help. Explain this to her, and assure her you are there to help.

3. Explore patient understanding and concerns

Ensure she is aware of the problem and try to explore her beliefs, concerns and expectations about the problem.

4. Attempt to discover the patient's reasons for not wanting to disclose

Is she scared about being diagnosed with HIV? If so, why? Is she scared for herself, or for the effect it will have on her family or marriage? Perhaps she knows that she has been exposed to HIV in the past and has always feared this sort of predicament. Is it possible that she has been diagnosed with HIV in the past but has been living in denial?

5. Share your concerns and desired management plan

Your first concern is that she may be infected with HIV in addition to hepatitis B. Try to let her see the importance of excluding or confirming the diagnosis. A supportive approach is essential, letting her see the potential advantages – the HIV test may be negative; were the test positive, it would allow earlier institution of treatment and testing of contacts (who could well be negative). Much better treatments are available for HIV than her friend would have received. Denial will not make the problem go away. She will know this, and her decision to avoid testing and telling is almost certainly motivated by fear.

6. Respond to patient cues

Continuously look for non-verbal as well as verbal cues.

7. Discuss possible consequences of refusal

In a non-threatening way, explain that you have a dilemma of interests. Whilst your first concern is for her, you are very concerned that in the event that she does have a positive test there are wider implications.

8. Confirm understanding

Ensure that she fully understands that your first duty is to her and not her husband, that you will not tell her husband, but that for the best steps to be taken for her health and the potential health of her family she needs to tell him.

9. Allow time to think about what has been discussed and invite questions

Allow her time to think about what has been discussed and to ask questions. She may have initially decided that the worst outcome would be for her husband to know that she has hepatitis or HIV. Your task has been to identify other outcomes for her to consider.

10. Agree a way forward

If she does not immediately agree, it is likely that she needs more time to contemplate what you have discussed and you should at least attempt to end the discussion with a plan to talk again.

Discussion

Why is confidentiality important?

Confidentiality is central to the trust that exists in the relationship between doctor and patient. This has been enshrined in doctors' codes of professional conduct including the Hippocratic Oath, the Declaration of Geneva and General Medical Council (GMC) Guidelines. Information that a doctor learns from a patient 'belongs' to that patient. From a legal point of view a patient's case records do not belong to that patient, but from an ethical point of view patients should have the right to determine in general who has access to information they provide. Respect for patient autonomy supports confidentiality and opposes paternalistic attitudes, common in the past, in which doctors 'knew what was in a patient's best interests'.

What is your legal commitment to respect confidentiality?

The general obligation is to keep patient information confidential. This obligation is not absolute; the law may allow or obligate breach of confidentiality, but any breach should only be to the relevant person or authority. The question of whether or not breach of confidentiality is legal is often a matter of balancing harm to the patient if confidentiality is breached against harm to others if it is not. The equation is seldom simple and the law sees a strong public interest in individual doctor–patient confidentiality being maintained.

GMC guidelines do not have the force of law but are taken seriously by the Courts.

Breach of confidentiality does not occur if a patient is not identifiable or if a patient has consented to disclosure of information.

Doctors have a duty to take reasonable precautions to prevent confidential information from falling into the wrong hands.

Under what circumstances might confidential information be disclosed?

These are outlined in Box 4.13.

Box 4.13 **Circumstances in which confidential information might be disclosed**

Circumstances in which confidential information *must* be disclosed

- When legally required by a Court Order
- When a statutory duty to statutory regulatory bodies, as in communicable disease notification and the reporting of births, deaths, abortions and work-related accidents
- In cases of national security such as terrorism or major crime prevention or in assisting in the solving of a major crime (although you may not disclose detailed information to police officers about any matter).

Circumstances in which confidential information *may*, at a doctor's discretion, be disclosed

- When a third party is deemed to be at risk of harm, e.g. at risk of contracting a serious infectious disease
- In the public interest, e.g. informing the Driver and Vehicle Licensing Agency in the case of a patient with seizures known to continue to drive illegally
- Through sharing information with the health-care team.

When disclosure of relevant information between health-care team members is clearly required for investigation or treatment to which a patient has agreed, the patient's explicit consent may not be required. Such sharing of information is not generally viewed by the law as breaching confidentiality. Examples include passing information to medical secretaries for typing and writing information on request forms for investigations.

Timing of disclosure

Breaching confidentiality should usually be the 'last resort'. The patient should be given an explanation as to why disclosure is intended, and the doctor must be able to justify the decision. Before disclosing, a doctor might sensibly seek advice from colleagues, professional bodies such as the British Medical Association, and their medical defence organisation.

What are the possible consequences of breach of confidentiality?

These include loss of trust and breakdown in doctor–patient relationship, disciplinary action by the GMC, investigation of serious professional misconduct by the GMC and civil legal action.

Does information remain confidential after death?

Yes, and information cannot be released without consent of the patient's executor or a close relative fully informed of the consequences of disclosure.

CASE 4.20 BREACHING CONFIDENTIALITY WHEN A THIRD PARTY MAY BE AT RISK

Candidate information

Role

You are a doctor on the renal ward.

Please read this summary.

Scenario

Re: Mr Joe Green, aged 25 years

Mr Green is a builder about to undergo a renal biopsy for suspected immunoglobulin A nephropathy. He tells you that he is hepatitis C positive but instructs you not to share this information with anyone else.

Your task is to discuss this with him and decide whether or not the biopsy should proceed.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Joe Green is a 25-year-old builder who has been diagnosed with probable glomerulonephritis following an episode of macroscopic haematuria. He has been admitted to hospital for further tests including a renal biopsy. He has previously been well but has sporadically taken intravenous drugs and has had multiple sexually transmitted diseases. He was tested for hepatitis C at the genitourinary medicine clinic 2 years ago and the test was positive (human immunodeficiency virus (HIV) being negative) but has not required any specific treatment. He was due for follow-up blood tests last year but did not attend. He was afraid of possible progression. His girlfriend works as a nurse at your hospital. She does not know he is hepatitis C positive and he is afraid that if this information is recorded she could conceivably have access to it. He will tell her about his hepatitis but now is 'not the right time.' He felt he should tell the doctor in case it affects his biopsy but does not want anyone else to know.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm his identity.

2. Establish rapport

There is potential conflict between his right to confidentiality and the potential risk to colleagues, especially the doctor performing the biopsy and those performing phlebotomy. Start by reassuring him that you will try to help.

3. Explore patient understanding and concerns

It is always best to gather information before reaching conclusions and deciding on a course of action. Ask more about his hepatitis C. How does he know that he has hepatitis C? How did he contract it? What investigations and treatments has he had so far? Who has been supervising his care? He may feel that these are irrelevant questions and that you do not need this information. Explain that it may be important in building a better understanding of his kidney problem and that a renal biopsy can be dangerous if liver function is impaired.

4. Attempt to discover the patient's reasons for not wanting to disclose

Is he scared about his girlfriend finding out because of the impact on their relationship or are there other reasons? You might explore why he has told you of his diagnosis but instructed that others not be informed. Exploring his fears may give you the answer.

5. Share your concerns and desired management plan

Your first concern is that he has a condition that could put colleagues at risk. Although all patients should be deemed potential sources of risk when performing invasive procedures knowledge of the condition is important both for taking extra vigilance with procedures and in his overall assessment. Certain forms of glomerulonephritis are more common in hepatitis C infection or with HIV (his last test was 2 years ago). A further concern is for his girlfriend. Explain that it would be important for the medical team involved in the procedure and in his management to know that he has hepatitis C, but that the information would go no further than those involved in his immediate care. Explain that it would be sensible to obtain up-to-date serology for hepatitis B and C and HIV to build up a better picture of his condition, institute early treatment if there is evidence of active disease, and reassure if results are unchanged. Explain why his girlfriend should know.

6. Respond to patient cues

Continuously look for non-verbal as well as verbal cues.

7. Discuss possible consequences of refusal

If he still refuses disclosure, explain that you may need to talk to colleagues on astrictly 'need to know' basis. Discussion with your medical defence organisation may be appropriate.

8. Confirm understanding

Ensure that he understands the reasons for his hepatitis being known, not least that he may be offered best treatment.

9. Allow time to think about what has been discussed and invite questions

Allow him time to think about what has been discussed and to ask questions.

10. Agree a way forward

The examiners are aware that such a discussion is difficult. They are not looking for a 'model answer' but checking your awareness of the range of issues provoked and ability to handle these sensitively and professionally. They would be more concerned if you found such a case clear cut and chose one of two extremes – agreeing to the patient's instructions or informing him that you intended to breach confidentiality without having had careful discussion around it. If he remains firm in his decision and refuses to allow disclosure, you may conclude that failure to inform some of your colleagues will place them at serious risk. It is then possible to breach confidentiality on the grounds of risk to others and on a strictly 'need to know' basis. You should inform him of what you propose to do.

Discussion

Does his girlfriend have a right to know?

A patient who has decided not to tell contacts at risk must recognise that this decision may have serious outcomes for these contacts and that breach of confidentiality would be a potential ultimate step. Persuading him to share that knowledge is preferable, and other possible routes could be to involve his general practitioner or his genitourinary medicine specialist, ideally with his consent.

A 32-year-old man has presented to your general medical clinic with weight loss and admits to a history of intravenous drug misuse and having multiple sexual partners. He is now living with his girlfriend, who is pregnant. You mention the possibility of HIV infection and he admits to having suspected this but adds 'if I had AIDS I would want to kill myself, doctor'. He also says that he feels angry. How might you respond?

It takes time to come to terms with the possibility of a serious diagnosis such as cancer or HIV infection, and very often anger is a secondary emotion, the primary one fear. At this stage you are not talking to him about having HIV infection, but about the importance of testing for it. Again, you should attempt to explore his fears, and find out why he would want to kill himself. It may be that to him HIV is a 'death penalty' and that he does not fully understand its natural history and current treatments. It may be appropriate to offer him a referral to trained HIV counsellors for further discussion of the implications of the test and its possible result. His partner and the fetus would be at risk and would warrant screening for HIV and the hepatitis B and C viruses if this patient were positive. There are also implications for the obstetric team. The difficulty is that this patient has not yet been tested. Although he has not refused to be tested, he has threatened self-harm should the test be positive. Hopefully, exploring his views and reaching a shared understanding of the problem may persuade him of the value of being tested and sharing the problem with his partner.

CASE 4.21 BREACHING CONFIDENTIALITY IN THE PUBLIC INTEREST

Candidate information

Role

You are a doctor in the neurology clinic.

Please read this summary.

Scenario

Re: Ms Holly Long, aged 22 years

Ms Long is a previously well student brought into hospital 6 weeks ago after a road traffic accident. She lost consciousness at the wheel and drove into a wall. She has had a normal ambulatory electrocardiogram and echocardiogram. She says she lost consciousness only transiently after she took a fizzy drink giving rise to severe heartburn. To build in evidence that this was likely to be situational syncope rather than seizure activity with an aura you feel she also warrants magnetic resonance brain imaging and an electroencephalogram. She is here for the results of her heart tests and is keen to drive again.

Your task is to talk with her.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Ms Holly Long is a previously well 22-year-old student brought into hospital 6 weeks ago after a road traffic accident. She lost consciousness at the wheel after a gulp of a fizzy drink with immediate heartburn and drove into a wall and has had subsequent tests to exclude a heart problem. She was told she could not drive until after the results. She is here for the results. She has a partner at a different university 100 miles away and desperately wants to be able to drive to visit him at weekends. She feels well and has decided to drive 'whatever the doctor says' and will tell him so.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Establish rapport

Your first duty is to her, analysing her perspective and how you may best help. Show this from the start.

3. Explain the results

Explain that the test results were reassuring. Explain that, whilst this is so, the tests do not exclude a seizure. Whilst physicians might not treat a first seizure, driving regulations do not permit driving within 12 months of unexplained loss of consciousness.

4. Explore patient understanding and concerns

Ensure she understands this and explore any difficulties it might pose.

5. Attempt to discover the patient's reasons for not wanting to adhere to advice

Show that you appreciate her concerns about not being able to drive to visit her partner.

6. Explain the risks and consider alternatives

Reiterate the dangerous accident she had, threatening both her own life and that of others. Are there alternatives to her, such as public transport? Ensure that she is aware it is only for a period of time.

7. Respond to patient cues

Continuously look for non-verbal as well as verbal cues.

8. Discuss possible consequences of refusal

In a non-threatening way, explain that you have a dilemma of interests. Whilst your first concern is for her, you are very concerned that, were she to continue driving, she might be at risk personally and legally, and be a risk to others.

9. Allow time to think about what has been discussed and invite questions

Allow her time to think about what has been discussed and to ask questions. She may have initially decided that the worst outcome would be for her not to be able to drive for 6 months. She may now see that taking your advice is, on balance, best.

10. Agree a way forward

Remember that patients have a right to a second opinion, although it may be appropriate to advise patients that some decisions are likely to be uniform amongst doctors, particularly where bound by a professional or legal framework.

Discussion

When may disclosure of confidential information be made in the public interest?

Personal information may be disclosed in the public interest without a patient's consent where the benefits to an individual or society outweigh the patient's interests in keeping that information confidential. Where there is a serious risk to patients or others, disclosures may be justified even where patients have been asked to agree to disclosure but have withheld consent. You should inform patients that disclosure will be made, where practical to do so. Ultimately, the public interest can be determined only by the Courts, and the General Medical Council may also require you to justify your actions.

What is the driving advice in medical conditions?

A person who drives with a medical condition has autonomy and a right to confidentiality. Yet breach of this confidentiality may be more important in the greater interests of benefit to society. The Driver and Vehicle Licensing Agency (DVLA) publishes a booklet on driving rules in medical conditions. A summary of rules for more common conditions is given below.

Seizures

Drivers with class 1 licences (non-heavy goods or public vehicles) must inform the DVLA after a first seizure. They must be seizure free for 12 months before they may drive, on or off medication. The DVLA may apply discretion and allow resumption of driving after a clearly provoked seizure (e.g. head injury); alcohol withdrawal does not qualify as provoked. The same 12-month restriction is invoked after any subsequent seizure. The restriction is for 3 years if seizures continue but are purely nocturnal. Patients should not drive for 6 months following any antiepileptic drug (AED) dose reduction, since there is a 40% risk of seizures occurring with drug withdrawal. This should be borne in mind with inpatients receiving AEDs; if a seizure occurs through inadequate prescribing then DVLA restrictions are fully imposed.

People with non-class-1 licences may not drive until seizure free for 10 years.

Syncope

The rules following syncope are outlined in Case 2.41 (Syncope).

Cardiac conditions

The rules depend on the condition. An acute coronary syndrome imposes a 4-week restriction (reduced to 1 week if successful percutaneous coronary intervention), and patients need not inform the DVLA.

Stroke/transient ischaemic attacks

A 4-week restriction applies if there are not considerable problems with weakness, vision or cognition. Visual fields should be at least 120° in the horizontal plane with no greater than 20° loss in up or down gaze. Formal field testing is needed if recovery is in doubt, unless the field is

Box 4.14 **Disclosure of confidential information to the Driver and Vehicle Licensing Agency (DVLA)**

- The DVLA is legally responsible for deciding if a person is medically unfit to drive and should know of a condition likely, now or in future, to affect safety.
- Patients should understand that their condition may affect the safety of themselves and others.
- Patients have a legal duty to inform the DVLA about their condition.
- If a patient refuses to accept the diagnosis or its safety implications, you should suggest a second opinion, assist the patient in obtaining it and advise them to refrain from driving until it has been sought.
- If a patient continues to drive when medically unfit, you should make every reasonable effort to dissuade them, which may include informing a next of kin.
- If this fails, you may disclose relevant medical information, in confidence, to the DVLA's medical adviser, informing the patient that you intend to do this.

clearly too compromised for driving, as in the case of a hemianopia or quadrantanopia.

Dementia

The rules in dementia are outlined in Case 2.44 (Mild cognitive impairment and dementia). Where a patient is deemed unsafe to drive by a doctor and may not have insight, memory or capacity to inform the DVLA, nor next of kin to do so, a doctor may inform the DVLA immediately.

Other

People with a variety of other medical conditions (e.g. diabetes on insulin, Parkinson's disease) must inform the DVLA of their condition.

When should you disclose confidential information to the DVLA?

This is outlined in Box 4.14.

CASE 4.22 CONFIDENTIALITY WHEN TALKING WITH RELATIVES AND OTHER THIRD PARTIES

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Peter Price, aged 34 years

Mr Price has muscular dystrophy and has been admitted to your ward with lobar pneumonia. He is stable but has a number of signs associated with a high risk (reduced consciousness, hypotension and leucopenia). His carer, who is not a relative, asks how he is. You also would value some background information about his home circumstances, quality of life and any prior expressed wishes in the event of this sort of situation.

Your task is to speak to the carer.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are a carer of Mr Peter Price, a 34-year-old man with muscular dystrophy. He has just been admitted to hospital with lobar pneumonia. His condition is unstable. You have cared for Mr Price for 4 years in his own home, but despite physical disabilities, notably his being unable to move his limbs, his general health has been very good. You are very anxious that he is now so unwell.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish the carer's identity.

> I'm sure you will understand that out of respect for (patient's name), I need to be sure to whom I'm speaking.

2. Acknowledge a valued contribution

Your primary responsibility is to the patient, whose medical details remain confidential. It is very easy to forget this when a patient is unable to speak. It is equally important, however, to respect the concerns of a third party and the valued information they can often provide. Show respect for the carer's expertise (and experience with this particular patient), and acknowledge the interdependence between patient and carer. The case records may be a valuable source of information and even demonstrate the patient's willingness for information to be shared with the carer.

3. Explain a little

State, in broad terms, that the situation is not good. Listen to responses and look for cues. It is remarkable how worried relatives and carers end up doing much of the talking and by disclosing very little you can often open the door to a lot of information from them. Frequently the relative or carer knows, or has suspected, a lot more than you may think.

4. Ask a little

Additional questions may open the door much wider!

5. Explain in more depth, directed by responses

You may then be in a position to speak more freely about the condition, again respecting your first duty to the patient and making sure anything you say is strictly information that will be of use to the carer in his or her role, and ultimately beneficial to the patient.

6. Involve the carer in the desired management plan

Involve the carer as far as you can in making decisions, without compromising the autonomy of the patient. Asking 'What do you feel he would want us to do?' is not asking the carer to make a decision but inviting his or her valued insights to help guide your own decision making.

7. Respond to cues

Continually look for non-verbal as well as verbal cues.

8. Consider other issues

It may or may not be appropriate, depending upon how well you feel the carer knows him, to establish whether the carer is aware of any prior wishes regarding resuscitation in the event of a cardiopulmonary arrest.

9. Allow time to think about what has been discussed and invite questions

Allow the carer time to think about what has been discussed and to ask questions.

10. Agree a way forward

Assure him or her that you will do all that you can to get the patient better, and that now you have established the carer's involvement you would be happy to update him or her at any time on the patient's progress.

Discussion

Under which circumstances may implied consent be sufficient for disclosure of confidential information to third parties?

Implied consent (Case 4.23) is appropriate for sharing information in the health-care team, provided that wishes are respected if a patient objects to a particular person or agency being made aware and this would not put others at risk, or when disclosing information for clinical audit, including identifiable information if patients have been informed that their information may be used for such purposes and have not objected.

Under what circumstances must express consent be sought to disclose information to third parties?

Express consent (Case 4.23), verbal or written, is needed for disclosure of information to a third party under most other circumstances, including to a nearest relative.

What type of consent is needed when disclosing information to third parties such as employers, police, lawyers and insurance companies?

Verbal consent from patients is usually sufficient when giving information to relatives, but written consent should be obtained when communicating with employers and in any legal matters. Patients must be aware of the purpose of disclosure, the obligation a doctor has to the third party and that this may include disclosure of personal information.

Can information about a patient be disclosed for education and research without consent?

Information about patients can be useful for such purposes as education, research, audit, administration, monitoring, epidemiology and public-health surveillance. Express consent is generally preferable for disclosure, whether or not it is judged that patients can be identified from the disclosure and even though disclosure is unlikely to confer personal consequences. Anonymised data without patient consent may be acceptable for education and audit, and in research where it is not practicable to contact patients a research ethics committee should decide whether the likely benefits of research outweigh the loss of confidentiality. Express consent should be sought when publishing material such as case histories or photographs of a patient, whether or not that patient is clearly identifiable.

An 80-year-old man has just recovered from a stroke. He lives independently and is to be discharged from your ward later this week. One of the nurses on your ward asks if you will speak to his daughter. You are asked by a woman over the phone, 'What has happened to my father?' Would you tell her?

You would establish the caller's identity. Clearly, if you have met her on the ward, recognise her voice, and know that her father has always been happy to share his medical problems with her, you would be less guarded. If you had no prior knowledge that he consents to divulging of information, you should explain why you could not without his permission.

The daughter now requests that you not tell him anything more about his condition without her prior permission – 'he is a worrier'. Would you agree to this?

You should not be willing to withhold information from him based solely on his daughter's wishes. You should explain that he has a right to know what has happened (respecting his autonomy) and to make his own decisions based on that information. You could reassure her that you would not force information on him, explaining only as much as he appeared to want to know. You might also suggest that discussion by phone is not ideal and offer to speak to her if she comes in to hospital to visit her father. You should avoid stating legal rights in these sorts of situations. Relatives never warm to being told 'I'm within my rights not to tell you'. Phrases like 'I share your concerns', 'I understand how concerned you must be', or 'I appreciate how you must feel' offer empathy and show that you are listening.

What are Caldicott Guardians?

Caldicott Guardians are senior people in NHS, local authority social care, and partner organisations, responsible for protecting the confidentiality of patient information and enabling appropriate information sharing.

CASE 4.23 CONSENT FOR INVESTIGATION OR TREATMENT

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Ms Kate Morland, aged 23 years

Ms Morland was admitted last night with a severe occipital headache of sudden onset. She is a normally fit and well young woman, who works at your hospital as a nurse. She sustained a minor whiplash injury 3 days previously in a minor road traffic accident. Her headache came on suddenly at a party. It was the worst headache she has ever experienced and reduced her to tears. Her computed tomography brain scan is normal.

Your tasks are to explain the reasons for performing a lumbar puncture (to exclude subarachnoid haemorrhage) and obtain her consent.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Ms Kate Morland, a 23-year-old nurse, was admitted to the emergency medical admissions unit last night with the worst headache she has ever experienced. She is a normally fit and well young woman, who works at this hospital. She sustained a minor whiplash injury 3 days ago in a minor road traffic accident. She is very scared. She has never felt this unwell. She is afraid that colleagues have witnessed her tears and distress. She has been told that a lumbar puncture is necessary but is afraid of further investigations involving needles and does not understand why she needs to stay in hospital because her brain scan was normal.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

She is very apprehensive, probably a cumulative effect of recent personal stresses, being admitted to her own workplace and fear of needles. Patients' fears are multiplied significantly if they feel, as they often do, uncertain about what is happening to them, what is planned and why. Establish an aura of calm. Explain that, before you do anything else, you would like to recap on the reasons for the scan, the desirability of doing one further test – the lumbar puncture – and to talk this through with her so that she can decide whether or not to go ahead. Make it very clear that in the last analysis it is her decision.

2. Explain the situation so far

Reassure her that the test results so far are good and that nothing bad, such as a brain tumour, has been seen. Explain the main unresolved concern.

> The main concern in this situation is the possibility of a small bleed, known as a subarachnoid haemorrhage. This is usually detected by the scan, but a small number of cases, perhaps around 10%, may not be picked up. Although it is generally small bleeds that are not picked up, the concern is that subarachnoid bleeds arise from a weakness in the wall of a blood vessel, and if not detected can recur with much more serious consequences. If detected, there are possible treatments to correct the underlying cause.

3. Explain the best way forward

> The only way to detect a smaller bleed is with a test called a lumbar puncture, these days a relatively straightforward test without too much discomfort.

4. Establish previous experience and be alert to ideas and concerns

Before explaining the test in more detail, establish any specific ideas or concerns. Many patients have heard exaggerated stories about lumbar punctures and big needles. Alternatively, she might have personal knowledge of someone close to her who had a difficult lumbar puncture for a serious disease.

5. Explain the nature of the investigation or treatment

Explain that a lumbar puncture involves, with local anaesthetic, a small needle inserted in to the lower part of the back to draw off spinal fluid. In the case of a subarachnoid bleed, this should be blood stained. She will need to lie curled up on her side during the procedure and remain in bed for around 4 hours afterwards.

6. Explain the risks and benefits of the investigation or treatment

Complications include headache (common) and much more rarely serious complications such as infection.

7. Explain any possible alternatives

In this case the alternative is to do nothing, because subarachnoid haemorrhage may be unlikely. Less optimal tests in patients at higher suspicion of subarachnoid haemorrhage who abjectly decline lumbar puncture might include magnetic resonance cerebral angiography, although this might only detect larger aneurysms.

8. Show respect for autonomy

In respecting her right to decide, you must be sure that she has been informed and understands that the test is ordinarily safe and straightforward and that the possible diagnosis, albeit unlikely, is potentially life threatening. Without telling a patient what must be done, it is crucial to explain that in your opinion a particular course of action seems to be in that patient's best interests.

9. Confirm understanding and invite questions

Allow her time to assimilate all of this information, confirm that she understands what you have explained and invite any questions.

10. Seek permission to proceed

Use an open question:

> How does this sound?

Discussion

What is consent?

Agreement to an action based on knowledge of what that action involves and its likely consequences.

What are the necessary requirements for valid consent?

Consent rests on the principle of respect for patient autonomy. For it to be legally valid three conditions must be met (Box 4.15).

What is battery?

A procedure performed without consent may be grounds for battery. Generally, if a person touches another without consent, this constitutes battery, for which damages may be awarded. Unlike negligence (Case 4.40), proof of harm is not necessary.

What is meant by implied and express consent?

Types of consent are discussed in Box 4.16.

Box 4.15 **Valid consent**

Requirements for valid consent

1. The patient should be properly informed.
2. The patient should understand that information and be competent (legally, have capacity) to give consent.
3. Consent must be given voluntarily, without coercion.

A written record of the conversation is necessary.

'Informed consent'

A patient needs a certain amount of information for consent to be legally valid. He or she must be aware of:

- The *nature of the intervention*; avoidance of *battery* requires that the doctor explains, in broad terms, the nature of the procedure
- The *risks and benefits, and alternative options or treatments*; this relates to the *avoidance of negligence*. In general, a doctor is not negligent if he or she has acted in accordance with the practice accepted as proper by a responsible body of doctors skilled in that art (i.e. what a responsible body of medical opinion would disclose in the same or similar circumstances). This is termed the Bolam test after the relevant legal case. However, the standard of information provision by doctors is evolving in English law, mainly as a result of General Medical Council guidelines, and is drawing nearer to the prudent-patient test widely used in North America. According to this test, doctors should provide the amount of information that a 'prudent patient' would want.

What most patients would want to know

For an investigation or treatment most patients would want to know:

- The possible or likely diagnosis, and its prognosis with or without treatment
- The purpose of the proposed investigation or treatment (furthering diagnosis, excluding serious diagnoses, improving prognosis)
- Any common or serious complications or side effects of the proposed investigation or treatment, and of the possibility of proposed treatment failing to produce the desired aim.

Box 4.16 **Types of consent**

Implied consent

Because touching a patient without consent can constitute battery, consent is needed even when, for example, taking a pulse or examining the chest. Yet doctors seldom obtain consent, either expressed orally or in writing, for such routine tasks, and in law patients could not successfully sue doctors most of the time because the Courts accept the concept of implied consent. If a patient offers their wrist while the doctor takes the pulse, consent is implied by their behaviour. However, the fact that a patient is in hospital for examination does not constitute consent to examination, investigation or treatment.

Express consent

Express consent, explicitly given (usually verbal but sometimes written), for investigation or treatment is preferable when:

- The investigation or treatment is complex or involves significant risks or side effects
- Clinical care is not the primary purpose of the investigation
- The investigation or treatment forms part of research
- There may be significant personal consequences for the patient.

Express consent may be oral or written, the latter a legal requirement in some circumstances, e.g. organ donation, and desirable where interventions are complex, there may be significant consequences on employment, social or personal life, clinical care is not the primary purpose of the intervention, or in research.

What information should be shared with a patient in order to obtain consent?

The exchange of information between doctor and patient is central to good decision making. How much information is shared with patients will vary, depending on their individual circumstances. The approach to discussion should be tailored according to:

- Their needs, wishes and priorities
- Their level of knowledge about, and understanding of, their condition, prognosis and the treatment options
- The nature of their condition
- The complexity of the treatment
- The nature and level of risk associated with the investigation or treatment.

Assumptions should not be made about:

- The information a patient might want or need
- The clinical or other factors a patient might consider significant
- A patient's level of knowledge or understanding of what is proposed.

Patients must be given the information they want or need about:

- The diagnosis and prognosis
- Any uncertainties about the diagnosis or prognosis, including options for further investigations
- Options for treating or managing the condition, including the option not to treat
- The purpose of any proposed investigation or treatment and what it will involve
- The potential benefits, risks and burdens, and the likelihood of success, for each option; this should include information, if available, about whether the benefits or risks are affected by which organisation or doctor is chosen to provide care
- Whether a proposed investigation or treatment is part of a research programme or is an innovative treatment designed specifically for their benefit
- The people who will be mainly responsible for and involved in their care, what their roles are, and to what extent students may be involved
- Their right to refuse to take part in teaching or research
- Their right to seek a second opinion
- Any bills they will have to pay
- Any conflicts of interest that the doctor or organisation may have
- Any treatments believed to have greater potential benefit for the patient than those the doctor or organisation can offer.

These matters should be explored with patients, with concerns listened to, views sought and respected, and that information is understood checked. Questions should be answered honestly and, as far as practical, as fully as wished.

How should information be shared?

The way information is communicated is as important as the information itself. It should be easy to understand and given with due consideration.

What would you do if a patient asks for decisions to be made on their behalf?

If a patient asks you to make decisions on their behalf or wants to leave decisions to a relative, partner or friend, you should explain that it is important that they understand the options open to them, and what the treatment will involve. If they do not want this information, you should try to find out why. If the patient still does not want to know in detail about their condition or the treatment, you should respect their wishes as far as possible. But you must explain the importance of providing at least the basic information they need in order to give valid consent to a proposed investigation or treatment. If the patient insists that they do not want even this basic information, you must explain the potential consequences of carrying out an investigation or treatment if their consent may be open to subsequent legal challenge. You must record the fact that the patient has declined relevant information and who they asked to make the decision about treatment. You must also make it clear that they can change their mind and have more information at any time. Apart from circumstances in which a patient refuses information, you should not withhold information necessary for making decisions, unless you believe that giving it would cause the patient serious harm.

Can a patient demand a treatment?

A patient with capacity may refuse a particular treatment but cannot demand a particular treatment that the doctor does not consider to be in that patient's best interests.

What exceptions are there to informed consent?

Exceptions are where a patient is judged not to have the capacity to give informed consent.

How might doctors be at risk of committing battery when obtaining consent from a competent patient?

By failing to give sufficient information about the nature of the procedure.

How might doctors be at risk of negligence when obtaining consent from a competent patient?

By failing to give sufficient information about common and rare serious side effects, benefits and possible alternatives.

A 65-year-old man has diabetic nephropathy as evidenced by microalbuminuria. You wish to start an angiotensin-converting enzyme (ACE) inhibitor. What type of consent would you obtain?

Rights are so basic yet so easily ignored. This is especially true of the right to consent to treatment or refuse it. In theory, consent should always be obtained for any treatment. In practice, there is often an implicit understanding that consent for examination, investigation or treatment is implied. Although such assumptions seldom result in problems, legal justification for them is not inevitable. You should obtain express consent, explaining why you feel the ACE inhibitor would be beneficial (knowledge of disease and its treatment), important side effects (knowledge of drug), any alternatives, and the risks or benefits and likely outcomes of these.

CASE 4.24 CONSENT AND CAPACITY

Candidate information

Role

You are a doctor on the stroke unit.

Please read this summary.

Scenario

Re: Mr Ashley Wills, aged 77 years

Mr Wills has been on your ward for 4 weeks following a left total anterior circulation infarct with dense right-sided hemiparesis, expressive dysphasia and a degree of receptive dysphasia. Over the past 4 weeks recovery has been minimal and his swallow, as assessed by the speech and language therapists, remains unsafe. At least one confirmed episode of aspiration has occurred. He has pulled out his nasogastric tube on numerous occasions and feeding has been erratic because it is difficult to replace. His serum albumin (although not reliably related to nutritional status) has fallen to 26 g/l. Your team feel that a percutaneous endoscopic gastrostomy (PEG) tube is in his best interests to support adequate nutrition and optimise potential recovery. It is increasingly likely that he will require long-term nursing care. You cannot be certain that Mr Wills understands or retains information.

Your tasks are to discuss with Mrs Wills, your patient's wife, why a PEG tube is being considered and obtain her consent.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Your husband, Mr Ashley Wills, is a 77-year-old man who has been on the stroke unit for 4 weeks following a large stroke with dense right-sided weakness and loss of speech. His comprehension of anything he is told is variable, and you cannot always be sure of what he understands. Over the past 4 weeks recovery has been minimal and his swallow remains unsafe. He is sometimes agitated, pulling out his nasogastric feeding tube on numerous occasions and his feeding has been erratic. You can see that his nutritional state is not optimal and the doctors have told you that this is confirmed on blood tests. The doctors feel that a percutaneous endoscopic gastrostomy (PEG), a feeding tube passed directly into the stomach, would support adequate nutrition and optimise potential recovery, but you have also been told that he is unlikely to get home again. Your husband has always feared 'ending up in a nursing home' and you are not sure that he would want further intervention.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduce yourself and establish the relative's identity

Introduce yourself and confirm that she is Mr Wills' wife.

2. Establish background knowledge

Find out what she understands about her husband's condition and the problems faced (rehabilitation challenges, nutrition compromised) to get an idea of where to start your explanation.

3. Explain the problem

Explain that the stroke has led to swallowing problems, preventing adequate nutrition and putting him at risk of further episodes of aspiration. Explain that he has pulled out the nasogastric tube on numerous occasions and that it has proved challenging to replace and that in any event this is not an ideal long-term solution to meeting his nutritional needs. Explain that with time and without adequate nutrition her husband will inevitably decline.

4. Explain possible solutions

Explain that one option is a PEG tube, and explain that this involves insertion of a small feeding tube directly into the stomach through the abdominal wall. This can be performed in various ways but the most common method is via endoscopic guidance, under local anaesthetic and with a degree of sedation. Explain the potentially serious complications (infection, perforation, death). PEG tubes carry a modest but significant mortality as well as significant morbidity.

5. Be alert to cues

You may perceive how she feels about your proposed strategies from non-verbal cues.

6. Ask how the relative feels, and how she thinks the patient would feel about this

Sometimes patients' relatives are reluctant to give a view because they feel it is too much responsibility for a loved one to take. More often, relatives have concerns. They simply want what is best for their loved one but find it hard to make decisions because there seem to be risks with every choice. Reassure her that you will always try to do what is in the patient's best interests, but that it is important to know if to her knowledge her husband might have had any strong wishes one way or the other.

7. Attempt to address concerns

Relatives struggle, understandably, to come to terms with major changes such as the likelihood of nursing home dependency. However, in coming to terms with this there are many smaller hurdles or decisions to be negotiated along the way. Apart from the general wishes of most people not to be ill or to face nursing care or mental incapacity, most will not have thought in detail and discussed specific wishes like PEGs and even with valid advance directives the devil is often in the detail. When faced with a choice between nutrition to optimise whatever recovery is possible and certain decline, most relatives will agree to a PEG tube unless decline seems inevitable even with nutrition, in which case doctors would not consider it.

8. Relative agrees or relative disagrees with what you see as in patient's best interests

Most relatives agree to PEG feeding if it is clinically indicated. In those uncommon circumstances where there is a major differing view between relatives and medical staff you should consider two possibilities. If you can be convinced that information provided by his wife confirms his advance refusal of consent to a feeding tube, this should be respected. If you cannot be convinced of this, and feel that these are exclusively his wife's wishes then you should resolve to seek further advice from senior colleagues and, ultimately, you may need to contemplate a course of action that is at odds with a relative's wishes but that is seen as in that patient's best interests by the medical team; such a course of action should generally be followed gently, allowing relatives time to question the issue themselves and see things from your perspective.

9. Confirm understanding and invite questions

Be clear that she understands the issues raised, and invite questions.

10. Agree a way forward

A likely way forward will be to request PEG insertion, with the understanding that this decision might be revised if he were to deteriorate in the next few days but proceed if he remains stable.

Discussion

What are the key aspects, based on case law, of capacity to give or withhold consent?

For a patient to give valid consent to a procedure or treatment, she or he must be *competent* or, *in legal terms, have the capacity* to do so. The key aspects of capacity are listed in Box 4.17.

Box 4.17 **The key aspects of capacity (the 'test' of capacity)**

Each of the following must apply for a person to have capacity:

1. The ability *to understand information* relevant to the decision (proposed interventions such as investigations or treatments, alternative options, the intervention's possible benefits and risks, and the consequences of non-treatment); the person should also of course believe that information to be true
2. The ability to *retain that information* (for how long depends upon what the information is)
3. The ability to *weigh up the information* to reach a decision
4. The ability to *communicate* a decision.

Incapacity must be proven. All adults are assumed by law to have capacity unless proven otherwise. Further, a person may not be globally competent or incompetent. It is 'function or decision specific'. For example, a patient may be capable of declining surgery but incapable of judging their safety at home. Capacity may also fluctuate over time. Even where capacity may be limited, a doctor has a duty to give an account in simple terms to a patient of what is being proposed. According to the Mental Capacity Act (below) a person lacks capacity if because of 'an impairment of, or a disturbance in the functioning of, the brain and mind' (which can be permanent or temporary) he or she is unable to fulfil any of the four criteria in Box 4.17.

Can any doctor (or health-care professional) judge a patient's capacity?

It is the personal responsibility of any doctor or health-care professional proposing an investigation or treatment to establish whether a patient has the capacity to give valid consent. Where incapacity is being judged it is wise to seek agreement from colleagues and other members of the team involved in the patient's care, and where there is any doubt to seek the opinion of a psychiatrist.

What do you know of the legal necessity to treat incapacitated patients?

The concept of necessity is that not only is a doctor able to give treatment to an incapacitated patient when it is clearly in that patient's best interests, but it is also common law to do so. This still only applies to treatment aimed to improve or prevent deterioration in health. If the patient is known to have prior objections to all or some parts of a treatment, doctors are not justified in proceeding, even in emergency situations. If incapacity is temporary (e.g. anaesthesia, intoxication, unconsciousness), doctors should not proceed beyond what is essential to preserve life or prevent deterioration in health.

How may doctors be guided when making decisions for a patient without capacity?

Doctors, not relatives, are responsible for making medical decisions about incapacitated patients. Any procedures requiring a consent form should be consented to by doctors, not a next of kin. Guidance when making decisions for patients without capacity is given in Box 4.18.

What are the key principles and innovations of the English Mental Capacity Act 2005?

The Mental Capacity Act provides a statutory framework to empower and protect vulnerable people who are not able to make their own decisions. It makes it clear who can take decisions, in which situations, and how they should go about this. It is underpinned by five key principles (Box 4.19).

Key innovations of the Mental Capacity Act are outlined in Table 4.2.

Does the Mental Capacity Act aid determination of best interests?

It provides a best interests checklist (Box 4.20).

'Best interests' can be particularly emotive in end of life care. Case law suggests that the 'intolerability' of treatment is not the sole test of whether treatment is in a patient's best interests. The term 'best interests' encompasses medical, emotional and all other factors relevant to the patient's welfare. A patient's best interests may be interpreted as meaning that a patient should not be subjected to more treatment than is necessary to allow them to die peacefully and with dignity.

Can incapacity be inferred from a particular medical illness or diagnosis?

No. Alzheimer's disease or any other dementia, for example, does not necessarily imply incapacity.

What do you know about legal representation for incapacitated adults?

Social services can provide *agency* or *appointeeship* for handling the financial affairs of an incapacitated adult. Doctors may sign letters confirming mental incapacity; psychiatrists may become involved where mental state assessment is challenging.

Power of attorney (PA)

PA gives someone the legal right to act on behalf of another. PA is only applicable for people who can understand and not for people with incapacity (compare with proxy decision making in Scotland). A solicitor, for example, may act as PA to sell your house while you are on holiday. PA formerly lapsed if a person became incapacitated but in 1985 a special type of PA known as *enduring power of attorney (EPA)* changed this. PA can be revoked. Sometimes PA representatives can try to take PA too far. PA does not give the right to make medical decisions, which remain up to the patient, or, if the patient is incapacitated, the doctor acting in the patient's best interests, except in those circumstances where *lasting power of attorney (LPA)*, which replaced EPA, has been invoked allowing for proxy decision making under the Mental Capacity Act.

Court of Protection / Court Appointed Deputies

Court of Protection (CoP) (now a system of Court Appointed Deputies) applies to circumstances in which EPA (now LPA) has not been given and a patient has become incapacitated. It is concerned mostly with property, and requires medical evidence. CoP applications can be made by a solicitor (usual) or the state (Director of Social Services). Solicitors then request details as to why a doctor feels that a patient is incapacitated. Many doctors (e.g. care of the elderly physicians) complete the forms where incapacity is clear (brief, layperson's language is acceptable, e.g. poor memory, deluded); psychiatrists are often involved where incapacity is not so clear. The Court

Box 4.18 **Guidance when making decisions for a patient without capacity**

Best interests

Doctors may act in what they see as a patient's *best interests*. The doctrine of necessity underpinning the treatment of people who lack capacity requires that there must be a necessity to act and that such action must be in the best interests of the person concerned. This is a grey area; traditionally it has been felt that *best interests will be served when a doctor acts in accordance with accepted medical opinion (Bolam test)*. When more than one option seems reasonably in a patient's best interests (including non-treatment) that which *least restricts that patient's future choices* should be chosen. However, the Mental Capacity Act now more clearly stipulates how best interests should be determined.

Advance decisions

Doctors may be guided by any expressed wishes or *advance decisions* made at a time when the patient had capacity. Losing capacity, such as losing consciousness, does not negate previous wishes and a valid and applicable advance directive (Case 4.28) overrides best interests if these are discrepant.

Legal proxy

If a patient has a legal proxy – a welfare attorney or guardian – this person must be consulted about cardiopulmonary resuscitation decisions. In England and Wales* the Mental Capacity Act allows people over 18 years of age who have capacity to make a lasting power of attorney (LPA), appointing a welfare attorney to make health and personal welfare decisions on their behalf once such capacity is lost. Before relying on the authority of this person, the health-care team must be satisfied that the patient lacks capacity to make the decision, a statement has been included in the LPA specifically authorising the welfare attorney to make decisions relating to life-prolonging treatment, the LPA has been registered with the Office of the Public Guardian and the decision being made by the attorney is in the patent's best interests. In England and Wales neither welfare attorneys nor deputies can demand treatment that is clinically inappropriate.

Those close to a patient

Where a patient has not made an advance decision or has a legal proxy, treatment decisions rest with the most senior clinician in charge of the patient's care. Decisions must be made on the basis of the patient's best interests. In order to assess best interests, the views of those close to the patient should be sought, unless this is impossible, to determine any previously expressed wishes and what the patient would be likely to consider of benefit. In reaching a decision, in England and Wales**, the Mental Capacity Act requires that best-interests decisions must include seeking the views of anyone named by the patient as someone to be consulted, anyone engaged in caring for the person or anyone interested in the patient's welfare. Under the Act, all health-care personnel must act in the best interests of a patient who lacks capacity. In these circumstances, it should be made clear to those close to the patient that their role is not to take decisions on behalf of the patient, but to help the health-care team to make an appropriate decision in the patient's best interests.

Independent mental capacity advocate

In England and Wales the Mental Capacity Act requires an independent mental capacity advocate (IMCA) to be consulted about all decisions about 'serious medical treatment' where patients lack capacity and have nobody to speak on their behalf. The definition of serious medical treatment includes circumstances where 'what is proposed would be likely to involve serious consequence for the patient'. An IMCA does not have the power to make decisions but must be consulted as part of the determination of the patient's best interests. The rights of an incapacitated patient to such principles as non-discrimination, confidentiality, liberty and dignity are of course identical to those of a patient with capacity.

*In Scotland the Adults with Incapacity (Scotland) Act 2000 allows people over 16 years of age, who have capacity, to appoint a welfare attorney to make decisions about medical treatment once that capacity is lost. The Sheriff may, on application, appoint a welfare guardian with similar powers. Before relying on the authority of a welfare attorney or guardian, the health-care team must be satisfied that the patient lacks capacity to make the decision (the terms of a power of attorney may state how incapacity is to be determined), the welfare attorney or guardian has the specific power to consent to treatment (a register of valid proxy decision makers is held by the Public Guardian), the decision being made by the attorney would benefit the patient and the attorney has taken account of the patient's past and present wishes as far as they can be ascertained. In Scotland, welfare attorneys and guardians cannot demand treatment that is clinically inappropriate. In Northern Ireland there is currently no provision for anybody to make decisions on behalf of patients who lack capacity, although those close to patients should be consulted where a best-interests decision is being made by the clinician in charge of the patient's care.

**In Scotland the Adults with Incapacity (Scotland) Act requires doctors to take account, so far as is reasonable and practicable, of the views of patients' nearest relatives and carers. In Northern Ireland, where there is no statutory provision for decision making for patients who lack capacity, it is nonetheless good practice to discuss decision making with those close to the patient in order to determine what would be in the best interests of the patient.

appoints a receiver (e.g. relative, accountant) who acts for the incapacitated person. CoP is not necessarily permanent because it depends more on behaviour than prognosis.

It is common to look after patients in hospital who are vulnerable and lack insight and capacity, for example the elderly woman who lives alone in her own house, has no close relatives and who wanders at night around the house putting on the gas, or outside on to the road. If she lacks insight, she may ask to go home and simply reject all of your concerns. Your responsibility is for her safety. It may be impossible to put in care at home at night and if she has progressive dementia without acute psychosis or depression transferring her to psychiatric care is only shifting the problem. She will probably need gentle ushering to a community hospital bed unless direct care-home

Box 4.19 **The five key principles of the mental capacity act**

1. People are assumed to have capacity unless proven otherwise.
2. Before deciding that someone lacks capacity, all steps should be taken to enhance his or her decision-making abilities.
3. Someone cannot be said to lack capacity simply because he or she is making what might be seen as an eccentric or unwise decision.
4. A person's best interests should always be taken into account in making a decision on his or her behalf.
5. The least restrictive option (of basic rights and freedoms) should always be used.

Box 4.20 **Determining best interests**

The person making a decision must:

- Consider when/if the person is likely to regain capacity
- Encourage patient participation (e.g. repeatedly pulling out a nasogastric tube may be indicative of wishes)
- Consider past and present feelings, previous beliefs and values and other relevant factors
- Consult others (account should be taken, where practicable and appropriate, of the views of at least one of: anyone named by the person to be consulted on matters of the kind; anyone engaged in caring for the person or interested in their welfare; any donee with lasting power of attorney (LPA) granted by the person; any Court-appointed deputy). For people who lack capacity and who lack a spokesperson (no relative, friend, carer, LPA or deputee) an independent consultee arrangement is possible.

Table 4.2 Key innovations of the Mental Capacity Act

Key innovation	**What it means**	
Definition of incapacity	A clear test of incapacity (see Box 4.17)	
Designated 'proxy' decision makers may act on behalf of someone who lacks capacity under two mechanisms	Lasting power of attorney (LPA)	A person who still has capacity may donate an LPA to one or more people. This is similar to enduring power of attorney (EPA) which preceded it, but allows for the donor's (that person giving power of attorney) care, including medical care, to be decided by the donee (that person given power of attorney) although an LPA cannot refuse life-sustaining treatment unless expressively given this power and is bound by advance directives (whilst these forms of proxy may become increasingly common, it is likely that most patients will continue to have no such provision)
	Court-appointed deputies	The Court can appoint a deputy or deputies who can make welfare, health and financial decisions on behalf of a person who lacks capacity but are not able to refuse consent to life-sustaining treatment. They can only be appointed if the Court cannot make a one-off decision to resolve issues
Development of two public bodies to support the statutory framework designed around the needs of those who lack capacity	A new Court of Protection	Has jurisdiction relating to the whole Act and final arbiter for capacity matters
	A new Public Guardian	Registering authority for LPAs and deputies
Greater emphasis on decisions being made in the patient's best interests	Applies both to doctors and to any proxy decision makers	
Three further provisions to protect vulnerable people	Independent mental capacity advocate	Someone appointed to support a person who lacks capacity but has no one to speak for them Makes representations about feelings, beliefs and values and brings to attention of decision maker relevant facts Can challenge decision maker
	Advance decisions to refuse treatment	Statutory support of advance directives and decision making (does not apply to any treatment a doctor considers necessary to sustain life unless strict formalities have been complied with that include a decision in writing that is signed and witnessed and that includes an express statement that the decision stands 'even if life is at risk')
	Criminal offence	For ill treatment or neglect of a person who lacks capacity
Clear parameters for research	Research may be lawful if approved by relevant bodies (e.g. ethics committees) and cannot be performed as effectively on those with capacity Carers or nominated third parties must be consulted and agree that patient would approve	

placement is available, with her general practitioner on board. Although not urgent, ultimately her house may need to be sold and other affairs attended to. Therefore, concurrently, assuming she has no LPA in a distant relative or in her solicitor, social services should be contacted to start CoP proceedings.

Does the Mental Capacity Act allow detention of patients?

It is only permitted if it is reasonably believed to prevent harm and measures must be proportionate to the likelihood of serious harm. 'Deprivation of liberty' paperwork needs to be completed as part of the justification for the decision, which may be a holding measure if specific sectioning under the Mental Health Act becomes appropriate.

What do you know about safeguarding vulnerable adults in hospital?

Vulnerable adults include those who lack mental capacity, those with cognitive impairment, those disabled mentally or physically, those with sensory impairment, those in institutions, those with no fixed abode and those socially isolated.

Vulnerable adult risk management involves case-specific management, often a multi-agency approach, and involving the patient as far as possible in decision making; where this is not possible and there are no relatives or carers, or if there are concerns about the motives of relatives or carers, an independent mental capacity advocate (IMCA) may aid decision making in best interests, making more robust the traditional doctor 'best interests' decisions. IMCAs may be helpful if there are major medical decisions or if care placement is being planned, and they have the right to use the CoP if they have concerns about decisions being proposed.

Sadly, vulnerable adults are often subject to abuse, most commonly by those 'caring' for them, often in institutions, sometimes in their own home; carers may not be aware of the abuse, and abuse is not always intended; sometimes it has become 'the norm' over many years, and sometimes the patient's needs outgrow well-intentioned carers or institutions.

Signs of abuse may be physical (e.g. bruises, pressure areas), behavioural (e.g. fear, avoidance), loss of financial assets or neglect (e.g. malnutrition, weight loss, dehydration, unkempt appearance).

The clinician's role is an index of suspicion, accurate record keeping, arranging any appropriate medical photography, multidisciplinary team liaison and referral to the hospital social services team (HSST). The HSST coordinates all subsequent investigation and referral to the adult protection (AP) team or the AP police who may determine whether or not an offence has been committed; the AP police take over investigation of any offence, and it is important for clinicians to share information on a need-to-know basis.

CASE 4.25 REFUSAL OF CONSENT

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Ms Eleanor Dashwood, aged 75 years

Ms Dashwood was admitted to hospital recently with pneumonia. During the course of investigations she was found to have iron deficiency anaemia and subsequently a hard rectal mass was discovered, most probably a carcinoma. She is asymptomatic. She is otherwise well and has no past medical history of note. She has now made a good recovery from her pneumonia and is keen to go home. She refuses any further investigations or treatments for the likely tumour.

Your task is to establish that this is her informed decision.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Ms Eleanor Dashwood is a previously well 75-year-old, independent woman admitted to hospital with pneumonia. She is recovering from this but during the course of her stay she was found to be anaemic and subsequently a rectal lump was discovered, most probably a cancer. She told the doctors she had no symptoms but in fact has had constipation and episodes of fresh rectal bleeding over the last 2 months. She has not told anyone because her husband developed similar symptoms a few months before his bowel cancer was diagnosed. His cancer had spread to the liver at diagnosis and was incurable. He died despite a complex array of investigations and treatments. She does not wish to 'go down the same route of hospitals and tests' and would prefer to let nature take its course, even if that means rapidly deteriorating like her husband. She will refuse any further investigations or treatments for the likely tumour.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and make it clear you are here to help.

2. Explain the situation so far

> As I think you know, you had a rather nasty pneumonia when you came in to hospital that has responded very well to antibiotics. But I think you also know that during the course of our tests we found that you were anaemic – that your blood count was low. We also discovered a lump, in the tail end, and this is very likely to be the reason for the anaemia, very possibly a lump that may not be nice … a form of growth.

She will be likely to acknowledge all of this and may either tell you she has thought about this and decided she does not want anything done or she may be a little more open to your thoughts and ask what you feel ought to be done.

3. Explain the best way forward

The best way forward for her can only be established in conjunction with her.

> That is for us to decide together. First of all, we would need to consider some further tests to try to establish accurately what it is.

4. Establish previous experience and be alert to beliefs and concerns

Her husband's experience is clearly pivotal in her decision. Acknowledge this.

> I understand. I do understand.

It may be that she imagines painful tests. It may be that she imagines only chemotherapy, about which she has heard so many dreadful things, but would consider an operation. There are many 'maybes'. The point is that, before respecting her wishes (autonomy) for no further tests, you must try to understand precisely what her position is and help to inform her. Her decision may already have been made. But you should try to discover the reasons she made it and whether or not she has sufficient information at her disposal to make an informed decision. She may choose not to receive any more information, but ideally informed consent to no treatment should be obtained and based upon discussion of the acceptability and effectiveness of the various options.

5. Explain the nature of the investigation or treatment

> I understand fully how you must feel. And I'll say immediately that we will respect any decision you make. I should also tell you that at this stage we are by no means certain of the diagnosis and that tests would help us to be more certain – and to more certainly know whether this is a very different situation from that of your husband. It may well be.
>
> Were we to investigate, I would recommend a scan of the tummy, and then very likely a biopsy of the lump – by asking one of our surgical colleagues to take a sample of tissue from the lump via a flexible telescope with a light on the end. We would then be in a much better position to know the best way forward.

6. Explain the risks and benefits of the investigation or treatment and the consequences of not pursuing matters

> The tests would be likely to tell us one of two things. Firstly, they might show that this problem is very well localised, and if that is the case then very possibly curable. Secondly if, and there is always the possibility, things were not as confined as we hoped, then we might well be able to predict future problems and take action to lessen these. One of the more immediate problems that can sometimes arise is a blockage in the bowel, which can be difficult, and far more difficult to treat if it happens without our prior knowledge. There is, of course, a possibility that the lump is not as worrying as we had thought, and that the anaemia is due to something very simple. It would be nice to know this.

7. Explain any possible alternatives

She may ask what would happen next if she chose not to pursue tests.

> The alternative is simply to let you go home, perhaps asking your doctor to keep a close eye on things, and arranging for you to see us again at any stage if you were to change your mind. Or we could see you here in clinic in a few weeks to have another talk about things. I would just say, however, that you are a healthy lady in all other respects, and that makes it much more likely that you would find the tests, and perhaps treatment, more straightforward.

Ask if she has any relatives or people close to her with whom she might wish to discuss options, or with whom she might wish you to talk. A common problem, however, is that relatives may take a different view and exert pressure on the physician to act. The primary emotion is almost always desire for the best management of the patient. The physician may explain (if the patient is happy for such a discussion) that the issue has been fully discussed in terms of likely benefits and risks and outcomes, and that as a result of this information an informed decision has been made by the patient. Occasionally, relatives may feel that the patient is unable to make the best decision ('she is old and does not know what is best') to which the physician must explain that there is no evidence she or he does not have the capacity to make informed decisions.

8. Show respect for autonomy

We will do our best, whatever you decide.

9. Confirm understanding and invite questions

Allow her time to assimilate all of this information, confirm that she understands what you have explained and invite any questions.

10. Keep the door open

If she still refuses ongoing investigation, make it very clear that you are happy to see her again. In this situation, where she will have a lot to assimilate, it might be sensible to arrange follow-up in clinic anyway, if she agrees. She might be more likely to miss out on potential treatments unless you set up possible avenues towards these.

Discussion

If a young woman with Graves' thyrotoxicosis wanted to pursue homeopathic treatment, even when the endocrinologist has recommended carbimazole, would you agree?

You may not have the facts in front of you, but feel she 'needs' more than homeopathic treatment. But it is vital to understand why she feels the way she does and explore her reasons for choosing homeopathy. She may have experience of homeopathy for other conditions, she may have been ready to consider carbimazole before learning of a dangerous side effect (leucopenia), and she may have considered other forms of treatment. You should talk to her about Graves' disease, its complications, the benefits and risks of treatment and the likely natural history without treatment. You might tell her you are unaware of any effective homeopathic treatments. Is it possible, if she is adamant that homeopathic treatment will help her, that she would consider conventional treatment as well? Failing this, might she accept switching to conventional treatment within a certain time limit if her approach fails. You would of course inform your consultant of any conversation and document your advice carefully.

You have been seeing a 50-year-old man with tuberculosis in the respiratory clinic. He wishes to pursue homeopathic treatment rather than continue with antibiotics. Would you agree?

There comes a point where collusion with a patient is wrong, clinically, ethically and legally. Here, you have not just to consider this man's autonomy, but risks to other members of the public from his active tuberculosis. Rather than approaching this dilemma in a dogmatic way, listening to the patient's reasons, beliefs and concerns may avoid confrontation. Perhaps the importance of antibiotic therapy has never been fully explained. Perhaps he has heard that homeopathy can help a wide range of respiratory conditions. Listening and simple explanation may be enough to persuade him of his misconception. Perhaps he feels that the antibiotics should have worked by now and is concerned that he is still coughing. Perhaps he is frustrated that he cannot return to work and needs to vent his feelings.

Can a patient refuse treatment, even to the point of death?

Refusal of consent is discussed in Box 4.21.

Box 4.21 **Refusal to give consent**

- Any adult with capacity, because of their right of autonomy or self-determination, may refuse investigation or treatment for reasons that are rational, irrational or for no reason.
- Legally, such refusal of treatment supersedes the sanctity of life.
- To treat in these circumstances would constitute trespass or battery.
- Existing consent may be withdrawn at any time and new refusal overrides prior consent.

An example of refusal of treatment with a potentially life-threatening outcome would be that of a patient who is a Jehovah's Witness refusing blood products for whom a blood transfusion might be lifesaving. Respect for autonomy (self-determination) means that this refusal must be respected. Notwithstanding this, if an individual chooses an option that not only contradicts what appears to be in his or her best interests and that most people would choose, but also appears to contradict that individual's previously expressed attitudes, then you would be justified in questioning the individual's capacity to make a valid refusal in order to exclude a possible depressed or deluded state.

CASE 4.26 DELIBERATE SELF-HARM

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Miss Jane Hughes, aged 22 years

Miss Hughes was admitted to the emergency medical admissions unit earlier today after taking an overdose of paracetamol. She reported taking 16 50 mg tablets 12 hours before admission, with the intention of committing suicide. Her paracetamol level was below the treatment line and liver function tests are normal including the international normalised ratio. She is now keen to go home. The ward nurse is concerned that she may be at risk of further suicide attempts, and although a psychiatry opinion has been requested this might not happen until tomorrow.

Your tasks are to explore the reasons for her suicide attempt, assess her current suicide risk and suggest a way forward.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Miss Jane Hughes is a 22-year-old primary school teacher with no medical history of note. She was admitted to hospital this morning following an overdose of 16 paracetamol tablets. She has recently moved to the area, having finished her teacher training last year, and although she has no history of psychiatric disease or suicide attempts herself in the past she has suffered recently 'in silence' from the death of her father and taken to getting excessively drunk with new friends in the area on week nights, and, increasingly, drinking alone. Last month one of her class children died in a road traffic accident and she has found herself ruminating over this a lot. She is 'a bright young thing' according to friends, and 'has everything going for her' but suffers from low self-esteem, which she knows is irrational. She has never had any delusions or hallucinations. She does not know why she took the overdose now, only that she told a friend who brought her to hospital. She just wants to go home and forget it happened. She is about to see the doctor.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and make it clear you are here to help.

2. Show empathy

Deliberate self-harm, unhappily, is an increasing problem for emergency services and it is all too easy to assume that 'just another overdose' has arrived, 'probably with no intention of significant self-harm'. Suicide is an escalating problem and no patient's intentions should be underestimated and every patient's case should be considered on its own unique merit. These cases are complex, and warrant psychiatric appraisal. All doctors should be able to make an initial assessment of the situation and the risk. Firstly, tell her that you are sorry she is in hospital and that you understand things must have been very difficult to have reached this stage.

3. Establish ideas and concerns

There are clearly background issues, which she may or may not allude to.

4. Assess patient following a suicide attempt

All doctors should be able to perform an initial psychosocial assessment following attempted suicide (Box 4.22).

5. Explain what should be done next

Reassure her that you are satisfied medically but that you are concerned for her overall welfare.

Box 4.22 **Assessment following attempted suicide**

Questions about the episode

- Events preceding the act
- Reasons for the act
- Suicide intent
- Any psychiatric disorders including previous suicide attempts
- Family history
- Coping resources and support network
- Whether ready to accept help

Factors suggesting suicide intent

- Act undertaken alone
- Act timed that intervention unlikely
- Precautions to avoid discovery
- Active preparation for attempt
- Preparations made anticipating death
- Leaving a note
- Failure to inform potential rescuers afterwards
- Admission of suicidal intent

Factors associated with an increased risk of further suicide attempts

- Male
- Under 19 or over 45 years of age
- Unemployment
- Separated, divorced, widowed or living alone
- Previous suicide attempts with admission to hospital
- Alcohol or drug problems
- Psychiatric disorder
- Chronic disease

6. Reassure that information given is confidential

Give absolute reassurance of this.

7. Reassure that the psychiatrist will help to identify problems

Explain that the reasons for seeking a psychiatrist's help are that it is not your area of expertise and that you wish to protect her from future self-harm by dealing with issues that hold her back so that she can get on with life.

8. Explain possible alternatives

She may ask what would happen if she chose not to wait to see a psychiatrist. This depends on your assessment of her risk. Options include trying to arrange for more immediate psychiatric assessment by a liaison psychiatrist or member of the liaison psychiatric team or to seek telephone advice from a psychiatrist as to whether it is felt that she could be allowed home with early review. If risk is sufficiently worrying, you should be honest with her and explain that you have a duty of care to ensure that she does not leave until she has seen a psychiatrist. Application of the Mental Health Act should be a last resort.

9. Invite further questions

Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward

The examiners are aware that such a discussion is difficult. They are not looking for a 'model answer' but checking your awareness of the range of issues provoked and ability to handle these sensitively and professionally.

Discussion

What would you do if a patient wants to leave hospital before being assessed by a mental health professional?

Doctors have a duty of care that includes protecting patients as best as possible from ongoing risk. If a patient refuses to stay for mental health assessment following an episode of deliberate self-harm, you should if possible make your own assessment of risk (see Box 4.22). If you are still concerned, you should try to persuade the patient to stay and if they still refuse you may detain them under common law pending formal psychiatric assessment. If you are satisfied that risk is low, you may allow the patient to be discharged with appropriate information to the general practitioner (ideally after telephone approval from and perhaps follow-up with a psychiatrist).

What does common law allow in the matter of detention or treatment of patients?

It allows doctors to act in a patient's best interests in emergency situations where consent cannot be given (patient unconscious or lacks capacity). It allows detention pending assessment or treatment against a patient's will if in that patient's best interests (by saving life or to ensure improvement or prevent deterioration of physical or mental health). It should be documented that you are treating in best interests under common law.

Can you detain or treat against a patient's will if they have capacity?

Detention or treatment against a patient's will under common law or under the Mental Health Act is not possible if a patient has capacity. To do so may constitute a criminal offence. Where there are doubts about capacity (which may be function specific rather than global and may change over time) and a patient is at risk it is usually better to detain and treat than not do so. In the case of deliberate self-harm, patients frequently do have capacity but you may equally be concerned that capacity is temporarily lost by a psychiatric illness such as depression and if your assessment deems a patient to be at serious risk then you are unlikely to be criticised. Detention and treatment may be given under common law.

Which aspects of the Mental Health Act are relevant to general medicine?

The Mental Health Act 1983 permits compulsory detention and/or treatment of patients with a mental illness and/or mental impairment of a nature and/or degree that requires inpatient treatment against their wishes. If a patient needs to be in hospital because of a risk to self or others he or she may be detained or brought into hospital if appropriate people agree. But the Act does not allow treatment of mentally impaired patients for physical problems against their will, even if the physical problem is a result of deliberate self-harm such as self-poisoning. Therefore psychiatrists, often asked to 'section' such a patient for compulsory treatment, cannot do so, although treatment may be given under common law. The Act does, however, allow treatment where a physical condition causes the mental condition, as in an organic psychosis. Relevant sections of the Mental Health Act are listed in Table 4.3. Although there is a different legal system in Scotland, the principles are the same.

The Mental Health Act was revised in 2008, and a key change is a wider definition of mental disorder, encompassing any disorder or disability of the mind.

Table 4.3 Sections of the Mental Health Act

Section	Provision
2	Allows assessment and/or treatment for up to 28 days Requires two appropriately qualified doctors and a social worker
3	Allows extension for up to 6 months (may follow 2)
4	Allows patient to be brought to hospital in an emergency Requires a doctor and social worker
5 (2)	Allows any registered (i.e. not Foundation Year 1) hospital doctor to detain an inpatient under the nominated hospital consultant if psychiatric assessment likely to be delayed Patient may be detained for 72 hours pending full Mental Health Act assessment Initiated by a form H1 that is submitted to the local Mental Health Act administration team Does not allow treatment of any kind, which must be under common law if a patient does not consent (herewith a 'best interests' decision based on presumed current incapacity allows attempted treatment)
5 (4)	Allows a nurse to detain for 6 hours pending the arrival of a doctor to detain under 5 (2)
136	Allows police to bring a patient to an accident and emergency department, where doctors may decide to informally assess or arrange for a Section 2 or 3

An elderly woman takes a lethal ingestion with the intention of suicide. She declines intervention. She is assessed by the psychiatric team who feel that she has capacity to make this decision. Would you accept this?

At first sight it may seem that any patient attempting suicide must lack capacity because of depressed mood but this is by no means necessarily so. Some patients do feel that life is so miserable for intractable reasons and see no hope, such that, notwithstanding possible depression, they have the capacity to decide they no longer wish to live. While every opportunity must be given to allow the patient to change their mind, and it must be clear that the patient fully understands the implications of the decision, if a psychiatrist has confirmed capacity and declared that the decision should be respected, the patient's autonomy should be respected.

End-of-life issues

CASE 4.27 END OF LIFE AND PALLIATIVE CARE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Sylvia Earnshaw, aged 85 years

Mrs Earnshaw was admitted to the ward 3 days ago following an attempt to pass an oesophageal stent. A decision that curative surgery would not be possible for her oesophageal cancer was reached on a previous admission. She was admitted because of drowsiness following the procedure (an intended day case) and the procedure was not wholly successful, unable to negotiate the distal end of the tumour, and a repeat attempt was not ruled out. However, since admission she has deteriorated with aspiration pneumonia, thus far not responding to antibiotics and is progressively drowsy.

Your task is to discuss the care now appropriate for Mrs Earnshaw with her son.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the son of Mrs Earnshaw, an 85-year-old woman admitted 3 days ago following an attempt to pass a stent into her oesophagus. You are aware that the procedure was to relieve symptoms, but not really sure if that means an operation to cure things will be possible at a later date. She was admitted because of drowsiness following the stent procedure (an intended day case) and since then she has become more breathless. You are very concerned that she is much worse than before she was admitted, and wonder what is happening to her.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish that he is Mrs Earnshaw's son.

2. Establish what the relative knows

Firstly, establish a rapport with a relative you have not met before, establishing what he knows, appreciating that relatives may either have been told little or have been afraid to ask for more information and may still have false expectations about the future.

> What have you been told so far about her condition?

3. Give a warning shot

This is largely a breaking bad news scenario, and before explaining her condition you should say that she is very unwell. A simple statement, followed by a pause, is enough.

> Your mother's condition is not good.

4. Explain the situation

Relatives sometimes then volunteer that they are aware of the overall prognosis, but that things have deteriorated more quickly than anticipated, but are sometimes very surprised. Be prepared for any scenario.

> Your mother has developed a rather nasty chest infection, almost certainly because of the growth in the oesophagus – the gullet – that means that she has been at very high risk of aspirating or regurgitating food and fluids and saliva down into her lungs. The procedure, as I know you know, was tricky and the gastroenterologist found it impossible to pass the tube beyond the growth.

5. Acknowledge distress and allow ventilation of feelings

Wait for his response before explaining more.

6. Identify and prioritise concerns

He will probably want to know what that means in terms of overall prognosis now.

> The fact that the growth was difficult to bypass is of course a real concern. I know the gastroenterologists had hoped that if they could alleviate the obstruction it might enable her to eat and drink for a time. And I know that they have not discounted the prospect of having a further attempt. But clearly, as more complications arise, it becomes harder to see a good way forward. The growth, as you can appreciate, has not been one amenable to removal, or cure, and any treatments have therefore been directed to keeping symptoms at bay for as long as possible.

7. Explain what is likely to happen

Explain that you will continue to treat the infection actively, but there are inevitably limits. Explain that if it becomes inevitable that she is not going to get better, it might be appropriate to switch treatment entirely to controlling pain and breathlessness. You might feel that that stage has already been reached, but at least allow him some time to come to terms with the sudden change in his mother's condition. It may be appropriate to discuss continuation of intravenous fluids for the time being.

8. Identify support networks

It is human to want to discover a little more about the practical implications to him such as what other family members may be nearby, how far it is for him and other family to visit and so forth.

9. Invite questions

Always do this.

10. Conclude with assurances

Always conclude with an assurance that you will do all that you can to keep her comfortable and always be happy to discuss the situation with him or any member of the family.

Discussion

What is meant by end of life (EoL)?

Patients approaching the end of their life need high-quality treatment and care that supports them to live as well as possible until they die, and to die with dignity. Providing treatment and care towards the EoL will often involve decisions that are clinically complex and emotionally distressing, and may involve ethical dilemmas and uncertainties about the law. Patients, according to General Medical Council (GMC) guidance on EoL care, are 'approaching the end of life' when they are likely to die within the next 12 months but this includes patients whose death is imminent (expected within a few hours or days) and those with:

- Advanced, progressive, incurable conditions
- General frailty and coexisting conditions that mean they are expected to die within 12 months
- Existing conditions if they are at risk of dying from a sudden acute crisis in their condition
- Life-threatening acute conditions caused by sudden catastrophic events.

What is meant by EoL care?

> *How people die will remain in the lasting memory of relatives, carers, and the health and social care staff who have cared for the dying person and so it is important that all staff recognise their responsibility to provide the best possible care at the end of life.*
>
> (DOH 2008)

EoL care helps all those with advanced, progressive, incurable illness, including dementia, to live as well as possible, until they die. It enables the supportive and palliative care needs of both patient and family to be identified and met throughout the last phase of life, including the last days of life and care after death. This includes management of pain and other symptoms and provision of psychological, social, spiritual and practical support.

EoL care generally applies to all patients who have a prognosis of less than 1 year. Patients with dementia are an exception as the time scale to reach EoL can be much longer. Therefore it is important to involve patients with dementia in decisions regarding EoL care whilst they still have the cognitive ability to make choices.

The National End of Life Strategy recognises that quality and choice in EoL care are far from equitable and sets out an ambitious, far-reaching agenda to address this, including:

- Promotion of public awareness and reducing taboos about death and dying
- High-quality, integrated care across all settings
- Identification of people approaching the EoL to be strengthened
- All people approaching the EoL and their carers to have their needs assessed and a care plan which records their preferences, including where they would wish to die
- Ensuring that care is well coordinated and can be accessed rapidly 24/7, aiming to avoid unnecessary emergency admissions to hospital
- Ensuring that health and social care staff provide sensitive and culturally and spiritually responsive care during the last days of life and after death
- Ensuring health and social care organisations provide readily available information on all local services
- Recognising the needs of carers and families
- EoL care training.

What do you understand by the term 'palliative care'?

This is the holistic care of patients with advanced, progressive, incurable illness, focused on the management of a patient's pain and other distressing symptoms and the provision of psychological, social and spiritual support to patients and their families. Palliative care is not dependent on diagnosis or prognosis, and can be provided at any stage of a patient's illness, not only in the last few days of life. The objective is to support patients to live as well as possible until they die and to die with dignity.

What principles govern EoL care?

The choices and priorities of the individual are central to all EoL care planning and delivery. Care planning must meet the wishes, beliefs and priorities of the individual patient. The patient is central to the care plan, and they and/or their carers should be involved from the outset. The care plan should be regularly reviewed as the patient has the right to change their plan at any time.

Important principles, outlined in GMC guidance on EoL care, are as follows.

Equalities and human rights

Patients who are approaching the end of their life must have equal quality of care, and they and those close to them receive dignity, respect and compassion. The Human Rights Act 1998 incorporates into domestic law the bulk of the rights set out in the European Convention on Human Rights (ECHR). Health professionals must be able to demonstrate that decisions are compatible with human rights set out in the Articles of the Convention. The rights in the ECHR that are most relevant to decisions about treatment and care towards the end of a patient's life are:

- Article 2: The right to life and positive duty on public authorities to protect life
- Article 3: The right to be free from inhuman and degrading treatment
- Article 5: The right to security of the person
- Article 8: The right to respect for private and family life
- Article 9: The right to freedom of thought, conscience and religion
- Article 10: The right to freedom of expression, which includes the right to hold opinions and receive information
- Article 14: The right to be free from discrimination in the enjoyment of these other rights.

Presumption in favour of prolonging life

Decisions concerning potentially life-prolonging treatment must not be motivated by a desire to bring about the patient's death, and must start from a presumption in favour of prolonging life. This presumption will normally require all reasonable steps to be taken to prolong a patient's life. However, there is no absolute obligation to prolong life irrespective of the consequences for the patient, and irrespective of the patient's views, if they are known or can be found out.

Presumption of capacity

The presumption is that every adult patient has the capacity to make decisions about their care and treatment. Lack of capacity must not be assumed.

Maximising capacity to make decisions

If a patient's capacity to make a decision may be impaired, they must be provided with all appropriate help and support to maximise their ability to understand, retain, use or weigh up the information needed to make that decision or communicate their wishes. Detailed guidance about maximising and assessing a patient's capacity may be found elsewhere in this book in the sections on consent and capacity.

Overall benefit

If an adult patient lacks capacity to decide, decisions made on that patient's behalf must be based on whether treatment would be of overall benefit to the patient and which option (including the option not to treat) would be least restrictive of the patient's future choices. Those close to the patient who lacks capacity should be consulted to help reach a view. The term 'overall benefit' describes the ethical basis on which decisions are made about treatment and care for adult patients who lack capacity. It involves an assessment of the appropriateness of treatment and care options that encompasses not only the potential clinical benefits, burdens and risks of those options, but also non-clinical factors such as the patient's personal circumstances, wishes, beliefs and values. GMC guidance on overall benefit is consistent with the legal requirement to consider whether treatment 'benefits' a patient (Scotland) or is in the patient's 'best interests' (England, Wales and Northern Ireland), and applies principles set out in the *Mental Capacity Act 2005* and the *Adults with Incapacity (Scotland) Act 2000*.

What sorts of ethical and legal issues arise in EoL decision making?

The most challenging decisions in this area are generally about withdrawing or not starting a treatment when it has the potential to prolong the patient's life. This may involve treatments such as antibiotics for life-threatening infection or renal dialysis, cardiopulmonary resuscitation, or 'clinically assisted nutrition and hydration' and mechanical ventilation. There are many ethical and legal considerations, which is why a multidisciplinary approach with emphasis on communication and individually tailored management is so important. Here are some examples:

- Advance decision making (Case 4.28)
- Cardiopulmonary resuscitation (Cases 4.29 and 4.30)
- Withholding and withdrawing treatment (Cases 4.32 and 4.33)
- Clinically assisted nutrition and hydration (Case 4.34)
- Respect for autonomy and choice
- The Mental Capacity Act 2005 and lasting power of attorney (LPA) (Case 4.24).

Do you know of any decision-making models in relation to EoL care?

GMC guidance on EoL care incorporates decision-making models for patients with or lacking capacity (Box 4.23).

What measures in the acute hospital setting help ensure good EoL care?

- Recognising and diagnosing EoL
- Advance care planning (ACP)
- Information, explanation and discussion with patient and family
- Treatment escalation plan (TEP) and Do not attempt resuscitation (DNAR) documentation
- Preferred priorities of care (PPC) documentation
- Advance decisions to refuse treatment (ADRT) and LPA
- The hospital e-discharge summary
- The End of Life Electronic register (Electronic Palliative Care Co-ordination System e.g. ADASTRA), a list of all EoL patients including their TEP/DNAR status and their PPC
- Assessment and reassessment of the situation and changing needs
- Liverpool Care Pathway or equivalent

Recognising and diagnosing EoL

Commonly used tools include:

- The surprise question: 'Would you be surprised if this patient were to die in the next 6–12 months?'
- Performance status
- The patient's choice to not have further treatment
- Symptoms and clinical observations: weight loss of 10% or more in 6 months; serum albumin < 25 g/l; rapid decline
- Would my patient now benefit from supportive and palliative care?
- More than three admissions in the last year for exacerbations of chronic illness.

Some EoL prognostic indicators in certain conditions are given in Box 4.24.

Advance care planning (ACP)

ACP is the process of discussing the type of treatment and care that a patient would or would not wish to receive in the event that they lose capacity to decide or are unable to express a preference. It seeks to create a record of a patient's wishes and values, preferences and decisions, to ensure that care is planned and delivered in a way that meets their needs and involves and meets the needs of those close to the patient.

As treatment and care towards the EoL are delivered by multidisciplinary teams often working across local health, social care and voluntary sector services, planning ahead as much as possible helps ensure timely access to safe, effective care and continuity in its delivery to meet the patient's needs. Patients whose death from their current condition is a foreseeable possibility are likely to want the opportunity to decide what arrangements should be made to manage the final stages of their illness. This could include having access to palliative care, and attending to any personal and other matters they consider important. If a patient has a condition that will impair their capacity as it progresses, they should be encouraged to think about what they might want should this happen. Advance care plans should be fully recorded and need to be reviewed and updated as the patient's situation or views change.

TEP and resuscitation decision patient-held record

These should be discussed and documented. Resuscitation decision-making is covered elsewhere. Degrees or limits of proposed treatment escalation should be discussed with patients or relatives, and creating TEP forms without doing so is a leading cause of complaint to hospital trusts. Whilst consent is not legally needed for withholding or limiting a treatment, this is a hugely contentious area and best practice calls for discussion with patients or those close to patients.

Preferred priorities of care (PPC) document

What are the patient's feelings on their disease, what concerns do they have, what goals are they looking to reach, do they understand their illness and its prognosis, and do they have particular care preferences, now and in the future?

PPC is a document that individuals hold and take with them. It enables them to write down their thoughts and choices. It facilitates continuity of care. It is not legally binding. You must consider the Mental Capacity Act (2005), and any person making a decision regarding care/treatment of a patient lacking capacity has to take into account any statement of wishes and preferences made previously.

Advance decision to refuse treatment (ADRT)

This is legally binding and comes into effect when an individual loses mental capacity. It can only be used to refuse treatment and applies to refusal of specific treatments such as intravenous antibiotics and assisted feeding. It cannot be used to refuse basic comfort care.

Lasting power of attorney (LPA) – health

This is a strong legal document held by the patient. An appointed person has power of attorney to deal with the ill person's health and welfare decisions.

The EoL register

This gives rapid information on the patient's illness, needs and wishes when critical intervention is being

Box 4.23 **Decision-making models for patients with or lacking capacity**

Patients with capacity to make a decision

- The doctor and patient make an assessment of the patient's condition, taking into account the patient's medical history, views, experience and knowledge.
- The doctor uses specialist knowledge and experience and clinical judgement, and the patient's views and understanding of their condition, to identify which investigations or treatments are clinically appropriate and likely to result in overall benefit. The doctor explains the options, setting out potential benefits, burdens and risks of each. The doctor may recommend a particular option, but must not put pressure on the patient to accept advice.
- The patient weighs up the potential benefits, burdens and risks of the various options as well as any non-clinical issues relevant to them, and decides whether to accept any of the options. They have the right to accept or refuse an option for a reason that may seem irrational to the doctor or for no reason at all.
- If the patient asks for a treatment that the doctor considers clinically inappropriate, the doctor should discuss the issues with the patient and explore the reasons for their request. If, after discussion, the doctor still considers that the treatment is inappropriate, they do not have to provide it. They should explain their reasons and any other options available, including the option to seek a second opinion or legal representation.

Patients lacking capacity to make a decision

- The doctor, with the patient (if able to contribute) and the patient's carer, makes an assessment of the patient's condition taking into account the patient's medical history and the patient's and carer's knowledge and experience of the condition.
- The doctor uses specialist knowledge, experience and clinical judgement, together with any evidence about the patient's views (including advance statements, decisions or directives), to identify which investigations or treatments are clinically appropriate and are likely to result in overall benefit for the patient.
- If the patient has made an advance decision or directive refusing a particular treatment, the doctor must make a judgement about its validity and its applicability to the current circumstances. If the doctor concludes that the decision or directive is legally binding, it must be followed in relation to that treatment. Otherwise it should be taken into account as information about the patient's previous wishes.
- If a legal proxy has been appointed to make health-care decisions for the patient, the doctor explains the options to the legal proxy (as they would do for a patient with capacity), setting out the benefits, burdens and risks of each option. The doctor may recommend a particular option that they believe would provide overall benefit. The legal proxy weighs up these considerations and any non-clinical issues relevant to the patient's treatment and care, and, considering which option would be least restrictive of the patient's future choices, makes the decision about which option will be of overall benefit. The doctor should offer support to the legal proxy in making the decision, but must not pressurise them to accept a particular recommendation.
- As well as advising the legal proxy, the doctor must involve members of the health-care team and those close to the patient as far as it is practical and appropriate. If the legal proxy does not have the power to make a particular decision, the doctor must take account of the proxy's views (as someone close to the patient) in the process of reaching a decision.
- Where there is no legal proxy with authority, and the doctor is responsible for making the decision, the doctor must consult with members of the health-care team and those close to the patient (as far as it is practical and appropriate) before reaching a decision. The doctor will explain the issues, seek information about the patient's circumstances and seek views about the patient's wishes, preferences, feelings, beliefs and values. The doctor may explore which options those consulted might see as providing overall benefit for the patient, but the role of those consulted is to advise about the patient's known or likely wishes, views and beliefs and they must not be given the impression that they are being asked to make the decision. The doctor must take the views of those consulted into account in considering which option would be least restrictive of the patient's future choices and in making the final decision about which option is of overall benefit to the patient.
- In England and Wales, if there is no legal proxy, close relative or other person who is willing or able to support or represent the patient and the decision involves serious medical treatment, the doctor must approach their employing or contracting organisation about appointing an independent mental capacity advocate (IMCA), as required by the *Mental Capacity Act 2005*. The IMCA will have authority to make enquiries about the patient and contribute to the decision by representing the patient's interests, but cannot make a decision on behalf of the patient.
- If a legal proxy or other person involved in the decision making asks for a treatment to be provided which the doctor considers would not be clinically appropriate and of overall benefit to the patient, the doctor should explain the basis for this view and explore the reasons for the request. If after discussion the doctor still considers that the treatment would not be clinically appropriate and of overall benefit, they are not obliged to provide it. However, as well as explaining the reasons for their decision, the doctor should explain to the person asking for the treatment the options available to them, including the option of seeking a second opinion and applying to the appropriate Court for an independent ruling.

Legal proxy refers to a person with legal authority to make certain decisions on behalf of another adult. Legal proxies include: a person holding a lasting power of attorney (England and Wales) or welfare power of attorney (Scotland), a Court-appointed deputy (England and Wales) or a Court-appointed guardian or intervener (Scotland). Northern Ireland currently has no provision for appointing legal proxies with power to make health-care decisions. Powers of attorney must be registered with the Office of the Public Guardian in England, Wales and Scotland. 'Carer' refers to the person supporting the patient and representing their interests in the consultation about their health and what might be needed in terms of any investigations, treatment or care. The term 'those close to the patient' means anyone nominated by the patient, close relatives, partners and close friends, paid or unpaid carers outside the health-care team and independent advocates. It may include attorneys for property and financial affairs and other legal proxies, in some circumstances.

Who it is appropriate and practical to consult will depend on, for example: a patient's previous request; what reasonable steps can be taken to consult within the time available before a decision must be made; and any duty to consult or prioritise specific people set out in relevant capacity laws or codes.

Box 4.24 **End-of-life (EoL) indicators**

Cancer

- Disease progression not amenable to treatment
- Involvement of major organs
- Worsening performance status
- Worsening functional ability

Neurology

- Motor neurone disease an EoL prognosis from diagnosis
- Parkinson's disease when drug treatment no longer effective
- Multiple sclerosis very difficult but dyspnoea, worsening pain, medical complications

Chronic obstructive pulmonary disease

- Forced expiratory volume < 30% predicted
- Long-term oxygen
- Right-heart failure
- > 6 weeks of systemic steroids in the last year
- Heart failure
- Dyspnoea at rest
- Failure to respond to drug therapy
- Renal function declining

Renal disease

- Conservative treatment, not dialysis
- Chronic kidney disease stage 5
- Symptomatic of renal failure

Dementia

- An inability to perform activities of daily living
- You would not be surprised if the patient died within the next 6–12 months
- 10% weight loss in the previous 6 months without other causes
- Recurrent infections and pneumonia
- Double incontinence
- No consistently meaningful verbal communications

considered. It is an easily accessible electronic Web-based register with information for out-of-hours services. Most patients are put on the system by their general practitioner. It allows existing choices to be implemented. It can prevent unwanted hospital admission. It is accessible on edit or view basis by staff involved in the patient's care. TEP/DNAR status and any PPC, ADRT and LPA may be entered. It is voluntary for the patient and needs the patient's consent.

Liverpool Care Pathway (LCP) for the dying person

The LCP (one of numerous for the dying) ensures equitable management and care of patients who are dying irrespective of diagnosis, situation (designed to be used in any setting and across settings if patients are transferred) and place of death. It is used in the last days of life when death is the expected outcome of this episode of care. It documents the process accurately and consistently (using a single record that replaces all notes/care plans and is used by all staff). It is endorsed in the End of Life Strategy.

The LCP comprises three sections – initial assessment and diagnosing dying, ongoing assessment, and care after death. The multiprofessional team must agree that the patient is dying and that two of the following apply: bed-bound; semi-comatose; only able to take sips of fluids; no longer able to take tablets.

The LCP is not incompatible with treatment of conditions that may relieve suffering such as pneumonia, or delivery of parenteral fluids, particularly where withdrawal of the latter at LCP induction may produce emotive concerns. It may of course be discontinued if a patient improves (around 10% of patients will live despite being on the LCP). The LCP is not a tool to hasten or stall death, but to provide comfort and dignity in situations where death is likely within a week. Goals of care with the LCP include:

- Communication with patient and family
- Current medication assessed and non-essentials discontinued
- As required subcutaneous drugs written up according to protocol
- Comfort measures
- Psychological insight/religious needs
- Ongoing care and support over the days needed
- Care after death.

Typical subcutaneous drugs include diamorphine 2.5–5 mg for pain, hyoscine 400–1200 μg for noisy secretions, midazolam 2.5–5 mg for agitation or restlessness and levomepromazine 6.25 mg for nausea and vomiting; these may be extended in doses over 24 hours in a syringe driver, if, for example, two or more boluses of medication are required. Discussing resuscitation and LCP decisions with the patient, or, where incapable, relatives, is imperative.

Which drugs may be used to alleviate pain in modern palliative care?

Some are listed in Table 4.4.

What is the doctrine of double effect (DDE)?

The DDE attempts to distinguish between harms intended and harms foreseen but not intended. The DDE raises concern that it may protect dangerous practice. The DDE states that an action (such as an increase in opioid dose) that the professional foresees may shorten life – but does not intend to have that result – is justified provided that the intention is to benefit the patient and not shorten their life. In the classic interpretation, a patient is in pain, a higher dose of opioid is given to relieve that pain, but at the same time in the belief that this may shorten life. The

Table 4.4 Drugs to alleviate pain in palliative care

Routine use	Opioids such as morphine or diamorphine are commonly used as long-acting regularly prescribed preparations (e.g. Zomorph) and short-acting preparations for breakthrough pain (e.g. Oramorph)
Renal disease	**Oral** If the eGFR is < 30, renally excreted opioids such as codeine, morphine and diamorphine should be avoided except in very small doses. Oxycodone is 90% excreted by the liver. Buprenorphine, fentanyl and alfentanil are 100% excreted by the liver. An analgesic step-ladder in renal impairment is: 1. Paracetamol (50% normal dose) 2. Tramadol (50% normal dose) or buprenorphine patch 3. Oxycodone (normal dose if eGFR > 30, 50% normal dose if eGFR 10–30) – immediate release Oxynorm and modified release Oxycontin If the eGFR is < 10, a fentanyl patch may be suitable, with immediate release buccal fentanyl for breakthrough pain. The latter is immediate, rather than older breakthrough drugs which could take 30 minutes to act, and available as a sublingual lozenge (e.g. Effentura) rather than the outmoded lollipop. Fentanyl may be fatal in opioid-naive patients in whom it is better to judge opioid requirements first of all with shorter acting drugs **Subcutaneous** Alfentanil may be used for immediate release (0.5–1 mg), or in a subcutaneous syringe driver **Syringe driver** A 24-hour syringe driver to alleviate symptoms in dying patients could include: • Alfentanil 250 μg (instead of morphine) • Glycopyrronium 200 μg (instead of hyoscine) • Midazolam 2.5 mg (not adjusted for renal impairment) • Haloperidol 0.5–1 mg (instead of levomepromazine)
Buprenorphine	This is generally used for those with renal disease or those with compliance or swallowing problems. It is available as 5, 10 or 15 μg/h Butrans patches over a week or as 35 μg Transtec patches; greater requirements than this may warrant switching to fentanyl
Pregabalin	Pregabalin is now first line for neuropathic pain, as is amitriptyline, but the latter has many side effects. Pregabalin is best started in low dose (25–50 mg). Serotonergic syndrome is a potential complication
Lidocaine	5% lidocaine patches are licensed for post-herpetic neuralgia and said not to provide deep skin penetration but, in practice, seem to help some patients with localised pain from, for example, bone metastases, and are relatively harmless
Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors	These have fallen from favour somewhat because of thrombotic risk but remain very useful in palliative care
Tapentadol	This is a novel synthetic opioid with some morphine agonistic action and substantial norepinephrine (noradrenaline) reuptake inhibition. It acts on spinal cord pain pathways; 50 mg is equivalent to 10 mg oxycodone, 20 mg morphine and 200 mg tramadol
Opioid-induced constipation	Methylnaltrexone blocks opioid receptors peripherally in the gut but not centrally and is highly effective in opioid-induced constipation

eGFR, estimated glomerular filtration rate.

Association for Palliative Medicine (APM) has provided position statements on the DDE and use of sedation at the EoL:

> *The DDE states that the risk of a potential, known (foreseen), unintended consequence or side effect of treatment is justified only if all the following criteria are met: the intended effect is good in itself; the clinician's intention is solely to produce the good effect; the intervention is proportionate to the situation; the good effect is not achieved through the bad effect.*

There is a misconception that morphine-related and sedative drugs bring about death more quickly, and that doctors both know this and in some way condone their use with the double effect. The APM refutes this claim. It knows of no credible evidence to suggest that a patient's life is shortened either by opioids or by sedatives when used in line with accepted palliative care practice. The APM believes that the DDE is unnecessary to justify the use of dosing regimens necessary to manage pain or distress in all but the most exceptional circumstances.

All medication used in palliative care, including sedative medication, is aimed at the relief of specific symptoms. Medication that is sedating in its effect should be used only if the symptom cannot be relieved with more specific interventions. Rarely, patients may experience distress when symptoms cannot be controlled even after exhaustive attempts with specific interventions. In these circumstances, some patients may require sedating medication to diminish awareness of their suffering. If medication is sedating in its effect, the dose should be monitored to ensure that it is the minimum required to relieve the patient's distress. Medication used in this way does not shorten life. Sedation in palliative care is thus sedation while the patient dies and is not sedating the patient to death. Morphine and related drugs are vital painkillers but are wholly unsuitable for use as sedation.

Consider a patient dying from a malignant brain tumour who develops pneumonia and respiratory failure. A ventilator may prolong life but may also delay an inevitable death. What courses of action are there?

Broadly, there are five options at the EoL (Box 4.25).

Is allowing a person to die different from killing that person?

Many people believe that there is a moral difference between killing someone and allowing that person to die but Rachels (1986) showed that the distinction is not necessarily clear, describing two cases. In the first, person A stands to gain a large inheritance if his 6-year-old cousin dies and sneaks into the child's bathroom and drowns the child in a way that will look like an accident. In the second, person B also stands to gain and plans to drown the child but, on approaching the cousin, the child slips and hits his head, falling face down in the bath; person B watches the child die. A kills; B allows to die; but there seems no moral difference here. The question of a moral difference becomes more relevant when applied to withholding or withdrawing life-prolonging treatments. The central idea is that if a doctor kills a patient the doctor causes the patient's death, but if a doctor allows a patient to die the patient's death is the result of disease or 'nature taking its course'. Thus, options 4 and 5 in Box 4.25 seem worse than 2 and 3, which are accepted medical practices. Option 1 is now uncommon. Options 4 and 5 are illegal, and arguments against euthanasia include palliative care obviating its need, concerns about manipulation or exploitation, and 'slippery slope' effects. Although emotionally it may be easier to withhold than to withdraw life-prolonging treatment, the British Medical Association and GMC have indicated that there are no legal, or necessarily moral, differences between the two.

Box 4.25 **End-of-life options**

1. The sanctity of life view – to ventilate and therefore prolong life whatever else may apply. He would probably die from progression of his tumour.
2. To withhold life-prolonging treatment – to withhold ventilation, for example. He would probably die from respiratory failure. This has sometimes in the past, but very contentiously, been considered 'passive euthanasia'.
3. To withdraw life-prolonging treatment – to ventilate then withdraw from ventilation. He would probably die rapidly on withdrawal of ventilation. This has sometimes in the past, but very contentiously, been considered 'passive euthanasia'.
4. Assisted suicide – this is illegal.
5. Active euthanasia (performing an action that results in a patient's death) – killing a patient for any reason is normally murder.

Have you heard of the Assisted Dying for the Terminally Ill Bill and, if so, what ethical issues does it raise?

This concerns deliberate acts to end life, not assisting in the natural dying process. The Bill was the subject of a House of Lords Select Committee Report. The idea of deliberately ending life brings intense ethical questions, notably concerning morality, the integrity of the medical profession and social implications of the effects of society permitting direct killing, and so weakening the prohibition against killing, which currently protects us all. Palliative care is concerned with enabling patients with advanced life-threatening conditions to live with the best possible quality of life until death. Clinical experience and research suggest that most requests for euthanasia or physician-assisted suicide arise because of poor symptom control, depression, poor social and family support and loss of autonomy. Palliative care focuses on improving these aspects of a patient's life and many of us believe that the Assisted Dying Bill and attempts to legalise physician-assisted suicide are ethically unsound, fail to appreciate the nature and scope of palliative care and undermine the progress made in the care of the dying in recent years.

One of your patients, a dying man with end-stage renal failure, diabetes and peripheral gangrene, has a hypoglycaemic attack. Would you treat him?

This would depend upon any prior wishes he may have made. He may have told his doctors to 'let him go' if he takes any turn for the worse. He may, alternatively, have declined treatment for his renal failure and requested a comfortable death. A scenario such as hypoglycaemia may not have been anticipated or explicitly discussed. A common response to a potentially fatal change in condition that has not been previously discussed is to treat the current episode and later discuss with the patient what they would wish were it to recur. This said, because hypoglycaemia, unlike other potentially fatal changes in his condition, is caused by the medication and easily reversed, there may be legal risks in not treating, whatever the patient says.

A woman has breast cancer with cerebral metastases. She asks you how many of her anticonvulsant pills she would need to take to end her life. How might you respond?

We sometimes hasten death in clinical practice. The crucial distinction is intention, which may be to hasten death or relieve suffering. Doctors may set out to relieve pain and suffering but see that life may be shortened. Foreseeing is not necessarily the same as intending. This has been tested in law and held to be permissible and in keeping with the duties of a doctor. It is one aspect of the DDE, which makes a distinction between harms that are intended and harms that are foreseen but not intended. Telling the patient how many pills she would require to kill herself could be seen as assisting suicide and a criminal act. Your communication skills should endeavour to elicit key aspects of her suffering as she sees them and explore alternative ways of relieving them.

CASE 4.28 ADVANCE DECISION MAKING

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Dr Max Winter, aged 79 years

Dr Winter is a retired microbiologist with chronic obstructive pulmonary disease (COPD). Four months ago he prepared an advance directive in conjunction with his family. This stated that in the event of worsening respiratory problems requiring admission to hospital he would not wish cardiopulmonary resuscitation or any form of ventilation including non-invasive ventilation. He was admitted to hospital a few minutes ago with an acute exacerbation of COPD and marked hypoxia. He is confused, probably a result of his hypoxia, and now says that he will accept any treatment to make him better, although this is at odds with his advance directive. The emergency team have ignored his advance directive and just instituted non-invasive ventilation, with apparently good effect. His wife wishes to discuss the advance directive with you.

Your task is to discuss his management with his wife, taking into account the issue of the advance directive.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are a retired general practitioner. Your husband, Dr Max Winter, is a 79-year-old retired microbiologist with chronic obstructive pulmonary disease (COPD). Four months ago he prepared an advance directive in conjunction with his family. This stated that in the event of worsening respiratory problems requiring admission to hospital he would not wish cardiopulmonary resuscitation or any form of ventilation including non-invasive ventilation. He was admitted to hospital a few minutes ago with an acute exacerbation of COPD and marked hypoxia. He is confused, probably a result of his hypoxia, and now says that he will accept any treatment to make him better, although this is at odds with his advance directive. The emergency team have ignored his advance directive and just instituted non-invasive ventilation, with apparently good effect. You have mixed feelings. On the one hand you are pleased to see your husband less distressed but on the other are concerned about his prior wishes being ignored. You wonder if the advance directive has any validity.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish that she is Dr Winter's wife.

2. Establish rapport and be alert to cues

Firstly, establish a rapport with a relative you have not met before, establishing what she knows, and if she does not volunteer the fact it may become clear that she is a professional colleague.

3. Seek further information about the patient

Relatives are highly valuable resources of information. She will know intimately the nature of his condition and his wishes in the event of a precipitous acute episode of illness.

4. Be sure that you understand the legal principles of advance decision making

Advance decision-making legal principles are discussed below.

5. Explain the situation

Be honest about what has happened. In this case there is a possibility that he is temporarily incapacitated by hypoxia and the previous advance directive, made when he had capacity, means there is a risk that the doctors applying non-invasive ventilation are committing battery. However, it seems very reasonable to have erred on the side of the possibility of his having changed his mind. Where there is uncertainty it is always preferable to make the choice that preserves future choice as much as possible. His wife will probably fully accept this, provided you are open with her and any Court (it would be very unlikely to go that far) would almost certainly see it that way, too!

6. Have a plan

The best way forward is likely to be to continue to treat non-invasively, stopping short of invasive ventilation, until her husband is able to competently confirm his wishes about any subsequent institution of non-invasive ventilation.

7. Ensure that your suggestions do not conflict with any ideas, concerns and expectations

Most importantly, ensure that she understands that where there was doubt the emergency team had little choice but to act in what they saw as being his current wishes or in his best interests but that you will be very sure to ascertain his wishes as soon as he is able to communicate these.

8. Seek acceptance of this plan

Highlight that the decision was ultimately that of the medical team, but that in future you will ensure that any unequivocal wishes will be confirmed and respected.

9. Invite questions

Make it clear that you are happy to answer questions now or later.

10. Conclude with assurances

Always conclude with an assurance that you will do your best to keep her husband comfortable and accord with his wishes as soon as these can be confirmed.

Discussion

What is an advance statement?

This is a statement of a patient's views about how they would or would not wish to be treated if they became unable to make or communicate decisions for themselves. It can be a general statement about, for example, wishes regarding place of residence, religious and cultural beliefs, and other personal values and preferences, as well as about medical treatment and care. Whilst not legally binding, such statements must inform best interests decisions.

What is an advance decision or advance directive?

This is a statement of a patient's wish to refuse a particular type of medical treatment or care if they become unable to make or communicate decisions for themselves. They are called advance decisions in England and Wales, and advance directives in Scotland. In England and Wales, advance decisions are covered by the Mental Capacity Act 2005. In Scotland and Northern Ireland, advance directives are not covered by statute but it is likely that they are binding under common law.

How might you act on advance requests for treatment?

When planning ahead, some patients worry that they will be unreasonably denied certain treatments towards the end of their life, and so may wish to make an advance request for those treatments. They may want a treatment that has some prospects of prolonging their life, even if it has significant burdens and risks. When responding to a request for future treatment the reasons for the request, and the degree of importance the patient attaches to it, should be explored. It should be explained how decisions about the overall benefit of the treatment would be influenced by the patient's current wishes if they lose capacity, and made clear that, although future decisions cannot be bound by request for a treatment, the request will be given weight by those making the decision. A patient's previous request, when benefits, burdens and risks are finely balanced, will usually be the deciding factor.

How might you act on advance refusals of treatment?

Some patients worry that towards the end of their life they may be given medical treatments that they do not want. They may want to make their wishes clear about particular treatments in circumstances that might arise in their future care. When discussing any proposed advance refusal it should be explained how such refusals would be taken into account if capacity is lost.

Binding advance refusals

An advance decision to refuse treatment (ADRT) states what a patient does not want to happen to them and must relate to a specific treatment and a specific circumstance. It comes into force when the patient loses capacity to consent to or refuse treatment. It is legally binding in England and Wales (and potentially binding in Scotland and Northern Ireland) if constituted according to the conditions in the Mental Capacity Act and if it meets the specific clinical circumstances. An ADRT for life-sustaining/life-prolonging treatment requires more rigorous legal criteria, and must be in writing, signed and witnessed and state that it should be enforced even if life is at risk. There are restrictions on an ADRT, for example that basic nursing care cannot be refused.

Non-binding advance refusals

Written and verbal advance refusals of treatment that are not legally binding should be taken into account as evidence of the person's wishes when assessing whether a particular treatment would be of overall benefit.

How might you assess the validity and applicability of advance refusals?

Assessment of validity and applicability is outlined in Box 4.26.

An elderly woman with dementia, living alone but with carers, fractures the neck of her femur. She is admitted to hospital with an abbreviated mental test score (AMTS) of 4/10. Her son says she would not wish any treatment. Would you agree to his request?

Regarding her autonomy, the patient is probably not competent and her AMTS is likely to represent a pot pourri of background cognitive impairment, pain and possible

Box 4.26 **Assessing the validity and applicability of advance refusals**

Validity

The main considerations are that:

- The patient was an adult when the decision was made (16 years old or over in Scotland, 18 years old or over in England, Wales and Northern Ireland)
- The patient had capacity to make the decision at the time it was made (UK wide)
- The patient was not subject to undue influence in making the decision (UK wide)
- The patient made the decision on the basis of adequate information about the implications of their choice (UK wide)
- If the decision relates to treatment that may prolong life it must be in writing, signed and witnessed, and include a statement that it is to apply even if the patient's life is at stake (England and Wales only)
- The decision has not been withdrawn by the patient (UK wide)
- The patient has not appointed an attorney, since the decision was made to make such decisions on their behalf (England, Wales and Scotland)
- More recent actions or decisions of the patient are clearly inconsistent with the terms of their earlier decision, or in some way indicate they may have changed their mind.

Applicability

The following considerations apply across the UK:

- Whether the decision is clearly applicable to the patient's current circumstances, clinical situation and the particular treatment or treatments about which a decision is needed
- Whether the decision specifies particular circumstances in which the refusal of treatment should not apply
- How long ago the decision was made and whether it has been reviewed or updated (this may also be a factor in assessing validity)
- Whether there are reasonable grounds for believing that circumstances exist which the patient did not anticipate and which would have affected their decision if anticipated; for example, any relevant clinical developments or changes in the patient's personal circumstances since the decision was made.

If there is doubt or disagreement about the validity or applicability of an advance refusal of treatment, further enquiries (if time permits) and a ruling from the Court may be sought. In an emergency, if there is no time to investigate further, the presumption should be in favour of providing treatment, if it has a realistic chance of prolonging life, improving the patient's condition, or managing their symptoms.

analgesia. On the principle of justice, most patients are more likely to do well with repair of their fractured neck of femurs and the benefits of surgery may outweigh the risks. It may be desirable to go ahead with treatment, with efforts to explain the rationale and get her family 'on board'.

A young woman with a history of asthma, necessitating multiple admissions to ITU, and depression is admitted with a further exacerbation of asthma requiring immediate ITU support. A handwritten letter in her notes addressed to her chest physician states that she wishes no treatment in the event of future collapse. Should she be admitted to ITU?

The answer is almost certainly yes. The validity of the advance decision may be in question for numerous reasons. It might have been written while she was depressed and her capacity might have been in question. The details may be sparse rather than specific. There may not be evidence that it was written by her. In case law there is a potential risk of battery if she receives treatment against the instructions of a valid advance directive but not treating puts her doctors at risk of manslaughter and because of the uncertainty the correct course of action is almost certainly to treat because of the uncertainty.

CASE 4.29 RESUSCITATION STATUS DECISION MAKING – DISCUSSION WITH PATIENT

Candidate information

Role

You are a doctor on the respiratory ward.

Please read this summary.

Scenario

Re: Mr Robert Churchill, aged 75 years

Mr Churchill has severe chronic obstructive pulmonary disease. He has a home oxygen cylinder. For the last 3 years he has been confined to his house, with twice-daily carers to assist with bathing, meals and housework. Breathlessness is his main limitation. Over the last year he has been admitted to hospital five times with increasing frequency and with exacerbations of breathlessness, sometimes precipitated by infection. Investigations for pulmonary emboli have been negative. He was readmitted yesterday with breathlessness and responded to initial non-invasive ventilation from which he has been successfully weaned. However, his resuscitation status has not been documented.

Your task is to discuss his resuscitation status with him. You may assume that you were involved in his care yesterday and on previous admissions and that he knows who you are.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Robert Churchill is a 75-year-old man who has severe chronic obstructive pulmonary disease. He has a home oxygen cylinder. For the last 3 years he has been confined to his house, where he lives alone, having been widowed for 5 years. He has twice-daily carers to assist with bathing, meals and housework. Breathlessness is his main limitation. Over the last year he has been admitted to hospital five times with increasing frequency and with exacerbations of his breathlessness. He was readmitted yesterday with breathlessness and required a tight breathing mask to improve respiratory distress. He is better today but knows things are not going to get any better in the long run. He has two children, but they live a long distance away. He has considered the future and 'doesn't want to go on indefinitely like this' but the issue of whether or not he should be resuscitated in the event of a cardiac or respiratory arrest has never been discussed.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction, setting and rapport

A discussion about resuscitation should be between a patient and ideally a doctor who has already created a rapport with that patient, even if brief. The setting should ideally be quiet, and without distractions.

2. Ensure the patient has enough information about their condition

A resuscitation discussion should only come once he has a full grasp of his condition and its likely prognosis even with treatment.

3. Then come directly to the reason for the discussion

> Mr Churchill, there is one thing I should discuss with you that relates to what we might do in the event – not that I'm expecting it – but in the event of things going very wrong (with your health) on this admission to hospital.

4. Pace the explanation slowly and carefully, and in words the patient will understand, allowing him to assimilate what you are saying

> You have been in hospital rather a lot over the last year, and now you're back in hospital sooner than you and your doctors had hoped. Someone with a lung condition as bad as yours may suddenly take a turn for the worse. I know you know this, having used the breathing apparatus last night and on other occasions in the past. We will of course do all that we can to improve the situation for you this time. But there is always the possibility, as with any unwell patient, that things could go very wrong: that the heart could stop, or the breathing stop, altogether. Have you ever thought about what your wishes might be in that situation?

5. Many patients immediately understand all of this, and pre-empt further discussion by declaring clearly pre-considered wishes. Some patients wish to go further and may ask about resuscitation

> If things were to go horribly wrong, and your heart or breathing were to stop, would you wish us to try to re-start things with heart-starting machines or breathing tubes and so forth?

6. Be prepared to deal with emotions before facts if you sense the discussion is causing distress

> I can see that you find this difficult. We could talk about it later, if you prefer, or, if you wish, with members of your family here (if you know there are family members) or some patients simply prefer that we do what we think is the very best for them.

7. Many patients prefer to leave the decision to their doctors

> I would leave it in your hands, doctor. Do as you think best.

8. Some patients might ask what you think

> Well, we would have great concerns that in the event of things getting to that stage, trying to rescue the situation would be in vain. It simply would not work.

It is not inappropriate to tell patients or relatives that you think resuscitation extremely unlikely to be successful or to be futile or that invasive ventilation would be very unlikely to bring recovery. Many patients do not appreciate, until it is explained, that resuscitation and the potential consequences of temporary revival without meaningful recovery or longer term survival might simply be increasing the distress of an inevitable natural death, prolonging death rather than sustaining life, or increasing the likelihood of 'two deaths'.

9. Confirm patient understanding and explore any other concerns

Ensure that he is clear about the course of action, be prepared to explore any other concerns and ask if he would like anything clarified.

10. Conclude with assurances

Always conclude with an assurance that, if a decision is made not to resuscitate, you and your team will continue to do all that you can to actively treat his condition and to relieve symptoms. Make it clear, where appropriate, that a decision can be reviewed and altered at any time.

> Meanwhile, we will do all that we can to get you better (up to the brink).

Discussion

Why is it important to consider cardiopulmonary resuscitation (CPR) decision making in advance care planning?

The primary goal of health care is to benefit patients, by restoring or maintaining their health as far as possible, thereby maximising benefit and minimising harm. If treatment fails, or ceases to benefit, or if an adult with capacity has refused treatment, that treatment is no longer justified. Prolonging a patient's life usually provides a health benefit to that patient. Nevertheless, it is not appropriate to prolong life at all costs with no regard to quality or to the potential burdens of treatment. The decision to use any treatment should be based on the balance of burdens, risks and benefits, and that principle applies as much CPR as to any other treatment.

CPR has a reasonable success rate in some circumstances but the survival rate after cardiorespiratory arrest and CPR is generally relatively low. After CPR for cardiorespiratory arrest that occurs in hospital, the chances of surviving to hospital discharge are at best about 15–20%. Where cardiac arrest occurs out of hospital, the survival rate is lower, at best 5–10%. The probability of success depends on factors including cause, how soon CPR is started, and equipment and staff available to deliver it. Attempting CPR carries a risk of significant adverse effects such as rib or sternal fractures, hepatic or splenic rupture, or prolonged treatment in an intensive care unit, possibly including prolonged artificial ventilation. There is also a risk that the patient will be left with hypoxic brain damage and resulting disability. And if CPR is unsuccessful, it may mean that the patient dies in an undignified and traumatic manner.

It is not uncommon for difficult decisions about CPR to arise in respect of patients for whom it may be possible to re-start the heart after cardiac arrest but for whom admission to an intensive care unit for continued organ support would be clinically inappropriate because they would be unlikely to survive that admission.

Do not attempt CPR (DNACPR) decisions

If cardiac or respiratory arrest is an expected part of the dying process and CPR will not be successful, an advance decision not to attempt CPR will help to ensure that the patient dies in a dignified manner. These management plans are called Do not attempt CPR (DNACPR) orders, or Do not attempt resuscitation (DNAR) or Allow natural death (AND) decisions. The overall clinical responsibility for decisions about CPR, including DNAR decisions, rests with the most senior clinician in charge of the patient's care. Any decision about whether or not to attempt CPR must be readily accessible to all health professionals who may need to know it. The person who makes a CPR decision is responsible for ensuring that the decision is communicated effectively to other relevant health professionals. Decisions about CPR must be reviewed regularly and especially whenever changes occur in the patient's condition or in the patient's expressed wishes.

Do you know of any CPR decision-making frameworks?

A CPR decision-making framework is shown in Table.4.5.

What is the 'presumption in favour of CPR' when there is no DNACPR decision?

There is always a presumption for protecting life and attempting CPR in unknown situations.

Emergencies

Emergencies can arise when there is no time to make a proper assessment of the patient's condition and the likely outcome of CPR, when no previous DNACPR decision is in place. If no explicit decision has been made in advance about CPR and the express wishes of the patient are unknown and cannot be ascertained, there should be a presumption in favour of CPR. In such emergencies there will rarely be time to make a proper assessment of the patient's condition and the likely outcome of CPR and so attempting CPR will usually be appropriate.

If further information comes to light

There may be situations in which CPR is commenced on this basis, but during CPR further information comes to light that makes continued CPR inappropriate. That information may consist of a DNACPR order or a valid and applicable advance decision refusing CPR in the current circumstances, or may consist of clinical information indicating that CPR will not be successful. In such circumstances, continued attempted resuscitation would be inappropriate.

Certainty of sufficient information to judge that CPR will not be successful

There will also be some patients for whom attempting CPR is clearly inappropriate, for example a patient in the final stages of a terminal illness where death is imminent and unavoidable and CPR would not be successful, but for whom no formal DNACPR decision has been made.

What is the approach to decision making when CPR will not be successful?

There are circumstances in which CPR will not to be successful or will be unlikely to be successful and, if successful, likely to prolong or increase suffering.

Table 4.5 Cardiopulmonary resuscitation (CPR) decision-making framework

Is cardiac or respiratory arrest a clear possibility in the circumstances of the patient?	No →	If there is no reason to believe that the patient is likely to have a cardiac or respiratory arrest it is not necessary to initiate discussion with the patient (or those close to a patient who lack capacity) about CPR. If, however, the patient wishes to discuss CPR this should be respected.
Yes ↓		
Is there a realistic chance that CPR could be successful?	No →	When a decision not to attempt CPR is made on these clear clinical grounds, it is not appropriate to ask the patient's wishes about CPR, but careful consideration should be given as to whether to inform the patient of the Do not attempt resuscitation (DNAR) decision. Where the patient lacks capacity and has a legal proxy, this person should be informed of the decision not to attempt CPR and the reasons for it. If a second opinion is requested, this should be respected wherever possible.
Yes ↓		
Does the patient lack capacity and have an advance decision refusing CPR or a legal proxy with relevant authority?	Yes →	If a patient has made an advance decision refusing CPR, and the criteria for applicability and validity are met, this must be respected. If legal proxy has been appointed they should be consulted.
No ↓		
Are the potential risks and burdens of CPR considered to be greater than the likely benefits of CPR?	Yes →	When there is only a very small chance of success, and there are questions about whether the burdens outweigh the benefits of attempting CPR, the involvement of the patient (or, if the patient lacks mental capacity, those close to the patient) in making the decision is crucial. When adult patients have mental capacity their own view should guide decision making.
No ↓		
CPR should be attempted unless the patient has capacity and states that they would not want CPR attempted.		

CPR will not be successful

In some cases, the decision not to attempt CPR is a straightforward clinical decision. If it is believed that CPR will not re-start the heart and maintain breathing, it should not be offered or attempted. However, the patient's individual circumstances and the most up-to-date guidance must be considered carefully before such a decision is made. The responsibility for making the decision rests with the most senior clinician, although they may delegate the task to another person who is competent. Wherever possible, a decision should be agreed with the whole health-care team. If there is genuine doubt or disagreement a further senior clinical opinion should be sought.

CPR unlikely to be successful and likely to prolong or increase suffering

When a patient is in the final stages of an incurable illness and death is expected within a few days, CPR is very unlikely to be clinically successful. In some cases it may prolong or increase suffering and subject the patient to a traumatic and undignified death. In these circumstances, most patients want a natural death without unnecessary interventions that most consider to be undignified. Earlier discussions with patients about their general care and treatment aims may have addressed this issue. The Liverpool Care of the Dying Pathway provides a comprehensive template of appropriate evidence-based multidisciplinary care for the last days of life and prompts clinicians to consider and document the patient's CPR status.

Communication

When the clinical decision is that CPR should not be attempted because it will not be successful, and the patient has not expressed a wish to discuss CPR, it is not necessary or appropriate to initiate discussion with the patient. Careful consideration should be given as to whether or not to inform the patient of the decision. Although patients should be helped to understand the severity of their condition, whether they should be informed explicitly of a DNACPR decision will depend on the individual circumstances. In most cases a patient should be informed, but for some, for example those who know that they are approaching the end of their life, information about interventions that would not be clinically successful will be unnecessarily burdensome. Others indicate by their actions and involvement in decision making that they want detailed information. Therefore an assessment should be made of how much information the individual patient (or, if the patient lacks capacity, those close to them) wants to know. If concluded that the patient does not wish to know about or discuss a DNACPR decision, their agreement should be sought to share with those close to them, with carers and with others, information they may need in order to support the patient's treatment and care. If a patient lacks capacity, any legal proxy and others close to the patient should be informed of the DNACPR decision and the reasons for it. A decision not to attempt CPR applies only to CPR. It must be made clear to patients, people close to patients and members of the health-care team that it does not apply to any other aspect of treatment.

What is the way forward if a patient requests CPR in situations where it will not be successful?

Neither patients nor those close to them can demand treatment that is clinically inappropriate. If the health-care team believes that CPR will not re-start the heart and breathing, sensitive efforts should be made to provide a realistic view of the procedure without causing undue alarm. If, ultimately, the patient or those close to the patient do not accept a DNAR decision in these circumstances a second opinion should be offered. Although a patient does not have a legal right to demand any treatment, including resuscitation, and the general requirement is for discussion rather than agreement, and although it might seem medico-legally more attractive to concord with such a patient's wishes, the ethical dilemma is that it may not seem in their best interests and resources could be put to the test in the unfortunate scenario of a concurrent cardiac arrest elsewhere for the team. In practice, fortunately, patients and doctors reach the same view the vast majority of the time, but if a patient explicitly requests resuscitation and the medical view is that it would not be of benefit then many doctors would choose to accord with that patient's wishes and make a sensible judgement about how far to take that resuscitation attempt at the time it happens, limiting any burdens and harms that may arise from resuscitation.

What is the approach to decision making when CPR may be successful?

These decisions are made by weighing up the potential benefits and burdens resulting from CPR.

Patients who have capacity

If CPR may be successful, the benefits of prolonging life must be weighed against the potential burdens and risks. This is not solely a clinical decision. Discussion must be sensitive and, if the patient is prepared to engage, informative of the burdens and risks, including likely clinical and other outcomes if CPR is successful. This should include sensitive explanation of the extent to which other intensive treatments and procedures may not be seen as clinically appropriate after successful CPR. For example, in some cases, prolonged support for multi-organ failure in an intensive care unit may not be clinically appropriate even though the patient's heart has been re-started. Any doubts the health-care team may have about whether the burdens and risks of CPR would outweigh the benefits, including whether the level of recovery expected after successful CPR would be acceptable to the patient, should be discussed.

A decision that CPR will not be attempted because the burdens outweigh the benefits should be made only after careful consideration of all relevant factors, discussion with the patient, or those close to patients who lack capacity, and these include the factors in Box 4.27.

Some patients may wish CPR when there is only a small chance of success, in spite of the risk of distressing clinical and other outcomes. If it is the considered judgement that CPR would not be clinically appropriate for the patient, the patient should have accurate information about the nature of possible CPR interventions, and the length of survival and level of recovery realistically expected if successfully resuscitated. The reasons for their request should be explored, with an attempt to reach agreement; for example, limited CPR interventions could be agreed in some cases. When the benefits, burdens and risks are finely balanced, the patient's request will usually be the deciding factor. If, after discussion, CPR is still considered not clinically appropriate, provision for it is not obliged. The reasons and any other options should be explained, including seeking a second opinion.

Some patients may, despite potentially distressing adverse effects, have specific reasons for wanting to try to delay death, even if this is only for a very short period of time. If such a wish is expressed, accurate information must be provided about the likelihood and length of survival that might realistically be expected, and about the potential risks and effects of attempted CPR.

Restriction of CPR to treatment of 'shockable' rhythms only is advocated by some clinicians in some specific clinical settings. Any such decision must be thought through clearly on the basis of the balance of risks, burdens and benefits to the individual patient and should be discussed with the patient (or those close to patients who lack capacity).

Box 4.27 **Factors to consider in weighing up the benefits and burdens of cardiopulmonary resuscitation (CPR) where CPR may be successful**

- The likely clinical outcome, including the likelihood of successfully re-starting the patient's heart and breathing for a sustained period, and the level of recovery that can realistically be expected after successful CPR
- The patient's known or ascertainable wishes, including information about previously expressed views, feelings, beliefs and values
- The patient's human rights, including the right to life and the right to be free from degrading treatment
- The likelihood of the patient experiencing severe unmanageable pain or suffering
- The level of awareness the patient may have of their existence and surroundings

Patients who lack capacity

The approaches are discussed in Case 4.30 (Resuscitation status decision making – discussion with relative).

What is the ethical and legal stance on refusal of CPR by adults with capacity?

Adults with capacity have the right to refuse any medical treatment, even if that refusal results in their death. Where health-care teams believe that CPR may be successful in re-starting a patient's heart and breathing for a sustained period, discussion should take place with the patient to determine their views and wishes regarding CPR. If a patient decides that they do not wish to have CPR attempted, this should be documented carefully and steps should be taken to ensure that this is communicated to those who need to know. Patients are not obliged to justify their decisions, but health professionals usually wish to discuss the implications of a refusal of treatment with patients in order to ensure that the decision is based on accurate information and not on any misunderstanding.

Advance decisions refusing CPR

CPR must not be attempted if it is contrary to valid and applicable advance decisions made when patients had capacity (Case 4.28 Advance decision making).

When might it be appropriate to temporarily suspend a DNACPR decision?

Uncommonly, some patients for whom a DNACPR decision has been established may develop cardiac or respiratory arrest from a readily reversible cause such as choking, induction of anaesthesia, anaphylaxis or blocked tracheostomy tube. In such situations CPR would be appropriate, while the reversible cause is treated, unless the patient has specifically refused intervention in these circumstances. It may also be appropriate to temporarily suspend a DNACPR decision during some procedures if the procedure itself could precipitate a cardiopulmonary arrest – for example, cardiac catheterisation, pacemaker insertion, or surgical operations. If a patient wishes an advance decision refusing CPR to remain valid during a procedure or treatment that significantly increases the risks of the procedure it would be reasonable not to proceed.

CASE 4.30 RESUSCITATION STATUS DECISION MAKING – DISCUSSION WITH RELATIVE

Candidate information

Role

You are a doctor in the acute medical unit.

Please read this summary.

Scenario

Mr Chris Ryder, aged 55 years

Mr Ryder has advanced Huntington's disease. For the last year he has required full-time care in a nursing unit with specialised psychiatric skills because of behavioural disturbance. He is not competent to make decisions for himself. He has been admitted with aspiration pneumonia and has worsening acute renal failure due to sepsis. Haemodialysis may be the only way to manage his renal failure in the short term, but in the context of his comorbidity you have to decide if this is appropriate. His sister is here to talk with you. She is not genetically affected.

Your task is to discuss the appropriateness of haemodialysis and intensive care, along with resuscitation status, with his sister.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the sister of Mr Chris Ryder, a 55-year-old man with advanced Huntington's disease. For the last year he has required full-time care in a nursing unit with specialised psychiatric skills on account of behavioural disturbance. He is not competent to make decisions for himself. You have lived with the knowledge of his inevitable decline for many years and anticipated situations from which he may not recover. You do not carry any risk of developing the disease yourself. He has now been admitted with aspiration pneumonia and has severe renal failure caused by his infection. Your brother did not make a written advance directive about his future wishes, but your feeling is that he would not wish to be kept alive if there were no possibility of long-term cure of the underlying cause. You are a trained nurse and feel that intensive-care transfer, if it came to that, would not be in his best interests.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish that she is Mr Ryder's sister.

2. Establish what the relative knows

Firstly, establish a rapport with a relative you have not met before, establishing what she knows, and what she thinks, before moving to a gentle explanation of where you are in terms of her brother's medical condition and possible ways forward:

What have you been told so far about his condition since admission to hospital?

3. Seek further information about the patient

Relatives are highly valuable sources of information. She may know intimately the duration and nature of his decline, his care needs and, in a chronic condition such as this, may well have anticipated what his wishes might be in the event of a precipitous acute episode of illness, and established her own views.

4. Do not forget empathy

No matter how pragmatic she may seem about his illness, remember that even expected declines often still strike harshly. Remain empathetic and pace your explanations slowly and carefully, and in words relatives will understand.

5. Explain the situation

Explain that his pneumonia is in itself treatable, but that it has provoked kidney failure that may or may not be recoverable. Explain that pneumonia is a more likely event in patients with advancing chronic conditions like Huntington's disease but that the kidney problem is now the most threatening. Explain that it is being managed with careful fluid replacement and monitoring of blood chemistry.

6. Approach the issue of more invasive interventions

> The next, very difficult question that I know you know I'm coming to is, if things were to deteriorate sharply, what we might do. We are treating as energetically, as vigorously, as we can, with fluids and antibiotics and by correcting the abnormalities in the blood which arise from the kidney failure. And we hope that things may improve. But he is at serious risk, and there is no getting away from that.

7. Ensure that your explanation does not conflict with any ideas, concerns and expectations

Most importantly, ensure that she understands that his life is threatened and if she makes it clear that she does and that she does not think that he would wish for more complex interventions it is appropriate to reinforce her views:

> I would have to agree. And my strong feeling and advice to you is that if there were further deterioration / a disaster, I would not be inclined to go down the route of dialysis or ventilators and intensive care … because I just do not think he would come through it. And the trouble is that even if he were to come through it all, without a clear way forward beyond all of this, without seeing him getting better, I think it would be putting him through unnecessary distress.

8. Many relatives worry that the decision is theirs and theirs alone

It may be important to highlight that the decision is ultimately yours, but that her views of what his wishes might be are highly valuable.

9. Confirm understanding and invite questions

Make it clear that you are happy to answer questions now or later.

Box 4.28 **Cardiopulmonary resuscitation (CPR) decision making in adults who lack capacity**

Advance decision or directive

A valid and applicable advance decision or directive should be respected (Case 4.28).

Legal proxy

If a patient has a legal proxy, this person must be consulted about CPR decisions. The rules governing the role and validity of the legal proxy are exactly the same for CPR decision making as any other treatment decision and are detailed in Case 4.24 (Consent and capacity).

Those close to the patient

Where a patient has not made an advance decision or appointed a legal proxy, the treatment decision rests with the most senior clinician in charge of the patient's care. Where CPR may re-start the patient's heart and breathing for a sustained period, the decision as to whether CPR is appropriate must be made on the basis of the patient's best interests. In order to assess best interests, the views of those close to the patient should be sought, unless this is impossible, to determine any previously expressed wishes and what level or chance of recovery the patient would be likely to consider of benefit. In reaching a decision in England and Wales the Mental Capacity Act requires that best-interests decisions must include seeking the views of anyone named by the patient as someone to be consulted, or anyone engaged in caring for the person or interested in the patient's welfare. Under the Act, all health-care personnel must act in the best interests of a patient who lacks capacity. In these circumstances, it should be made clear to those close to the patient that their role is not to take decisions on behalf of the patient, but to help the health-care team to make an appropriate decision in the patient's best interests.

Independent mental capacity advocate (IMCA)

In England and Wales the Mental Capacity Act requires an IMCA to be consulted about all decisions about 'serious medical treatment' where patients lack capacity and have nobody to speak on their behalf. The definition of serious medical treatment includes circumstances where 'what is proposed would be likely to involve serious consequence for the patient'. It can be argued that a decision not to attempt CPR because it will not work will not have 'serious consequences' for the patient, because the patient will die with or without attempting CPR. For this reason, an IMCA does not need to be called when it is clear to the medical team that CPR would not be successful. Where there is genuine doubt about whether or not CPR would have a realistic chance of success, or if a DNACPR decision is being considered on the balance of benefits and burdens, in order to comply with the law an IMCA must be involved. If a DNACPR decision is needed when an IMCA is not available (for example at night or at a weekend), the decision should be made, recorded in the health record and discussed with an IMCA at the first opportunity. An IMCA does not have the power to make a decision about CPR but must be consulted as part of the determination of the patient's best interests.

10. Conclude with assurances

Always conclude with an assurance that if a decision is made not to resuscitate, you and your team will continue to do all that you can to actively treat his condition and to relieve symptoms. Make it clear, where appropriate, that a decision can be reviewed and altered at any time.

> But we will do all that we can, keeping a very close eye and treating all that is treatable here on the ward. And we are here, if there are any questions at any time.

Discussion

What do you know about cardiopulmonary resuscitation decision making for adults who lack capacity?

The possibilities are described in Box 4.28 and more detail on treating adults who lack capacity is in Case 4.24 (Consent and capacity).

CASE 4.31 APPROPRIATENESS OF INTENSIVE THERAPY UNIT TRANSFER

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Angela Elliot, aged 62 years

Mrs Elliot has advanced multiple sclerosis. She is immobile, dependent upon carers for transfer from her wheelchair to bed, and unable to feed herself. Bulbar function is significantly impaired whenever she has intercurrent infection, its recovery following episodes is incomplete and she can only just tolerate a strict diet. Percutaneous gastrostomy feeding was being considered. Unfortunately, she has been readmitted to hospital with her fourth episode of pneumonia in 12 months. On this occasion admission to the intensive therapy unit (ITU) was considered for the first time, but because of a lack of ITU beds she was observed carefully by the ITU outreach team and 'made it through the night' with high-flow oxygen, suction and antibiotics. She is slowly improving, and no longer breathless. The nursing team have questioned whether she should be considered for ITU next time she has pneumonia, as Mrs Elliot has apparently expressed concerns about 'going on a ventilator' and would like to speak to a doctor.

Your task is to address her concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Angela Elliot is a 62-year-old woman who has advanced multiple sclerosis. She is fully dependent upon carers for transfer from her wheelchair to her bed, and unable to feed herself. She can swallow food, albeit very carefully prepared and of the right consistency, but swallowing is further impaired each time she is unwell. Percutaneous gastrostomy feeding has been considered and is acceptable to her. Unfortunately, she has been readmitted to hospital with her fourth episode of pneumonia in 12 months. On this occasion admission to the intensive therapy unit (ITU) was considered, but she 'made it through the night' with oxygen, chest physiotherapy and antibiotics. She is slowly improving, and no longer breathless. She has great concerns about a ventilator because she does not want to be 'kept alive indefinitely on an artificial machine'. Her daughter died after spending 4 months in an ITU following a road traffic accident. She has no other children, and is widowed. She would like to discuss whether ITU would really benefit her in future if this happens again. She has a fear of being ventilated only to die at the end of months of distress.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction, setting and rapport

Introduce yourself and state that you are glad to see her feeling a little better. Make it clear that you will do everything you can to continue to make her feel comfortable, and treat the chest infection.

2. Acknowledge how unwell the patient has been

Mention that you know how unwell she has been, and that, while you feel she should continue to improve on this occasion, she came very close to needing ventilatory support.

3. Explore the patient's concerns

Mention that the nursing staff have told you she had some concerns at being treated in intensive care. Explain that while you are always happy to consider what seems the best treatment at the time, it would be important to know if she has any strong feelings one way or the other about any specific measures, including intensive care.

4. Address the patient's concerns

Patients with long-term conditions have often given thought to what their wishes might be in the event of hypothetical clinical circumstances. While some patients would 'want everything done', many are very clear about circumstances they would not wish to occur, and this is very likely to include being artificially ventilated when there is no prospect of recovery (doctors would be unlikely to offer such a treatment in any event). The difficulty is that medicine is seldom clear-cut, and the prospect of recovery is often a case of best judgement rather than absolute certainty one way or the other. It is reasonable, provided the patient wishes it, to consider ventilation when there is a reversible acute cause for respiratory failure such as infection, but the balance of favouring to ventilate is progressively tempered as worsening of the underlying condition thwarts the likelihood of successful weaning from ventilation, and ultimately ventilation is tilted out of favour. Patients may choose not to be ventilated even when the balance seems to be in their favour, provided this is an informed choice. Occasionally, patients will feel guilty about refusing an option that may prolong their life, especially if they have close relatives. Ventilation may carry the prospect of recovery from future infective exacerbations, but the patient will judge if the extent of that recovery is something she wishes to be brought back to. ITU would, of course, decline admission when recovery does not seem likely. Increasingly, non-invasive ventilation has been an alternative to invasive ventilation and can be applied outside ITU, but its best evidence is in the setting of chronic obstructive pulmonary disease (COPD) exacerbations.

5. Discuss resuscitation status

It is often, but not inevitably, appropriate to discuss resuscitation status. Such discussion is usually a logical and natural extension if you have reached a decision about ITU being inappropriate, but should be discussed sensitively.

6. Ensure that the patient is fully informed

If a decision is to be made not to admit to ITU in future, especially if there is still a prospect of ITU benefit outweighing risk, ensure that this is made with adequate understanding of the alternatives and the consequences, and formed without coercion or undue influence.

7. Agree a plan

Agree to respect her informed choice.

8. Confirm understanding

Ensure that she is clear about the course of action and be prepared to explore any other concerns.

9. Invite questions

Ask if there is anything she would like clarified.

10. Conclude with assurances

Always conclude with an assurance that, if a decision is made not to admit to ITU in future, you and your team will continue to do all that you can to actively treat her condition and to relieve symptoms.

Discussion

Which patients fare better in ITU, and which worse?

The role of ITU is largely in support whilst primary therapy works. There is often a sense of ITU being inaccessible or unassailable to physicians outside it, but studies have shown that the often 'poor prognostic' pessimism of ITU physicians is not always thoroughly founded. For example, being old, being immunosuppressed or having malignancy have all been shown to have good outcomes with ITU where appropriate patient selection occurs. It does, however, seem clear that poor candidates for ITU generally are those with a combination of severe illness, a poor level of pre-morbid function (e.g. chair- or bed-bound) and multi-organ failure. However, it can be difficult to make physiological and ethical judgements at the same time and early, collaborative decision making between physicians and intensivists is to be encouraged.

Is invasive ventilation contraindicated in COPD?

Invasive ventilation is more likely to be appropriate where there is a reversible cause and an acceptable quality of life or habitual level of activity. Each case must be assessed individually. COPD is not a blanket reason not to ventilate because of fears about weaning. You should get an idea, for example, of how much oxygen is required at home or what is meant exactly by 'housebound'. Invasive ventilation may be appropriate for a remediable acute cause, if there is no significant other organ failure, for a first episode of respiratory failure or if the patient has made an informed wish for it to be attempted, whereas it would be inappropriate for a patient with end-stage COPD and a high pre-morbid arterial pCO_2.

How does age affect ITU outcome?

Around 25% of ITU admissions are of patients over 75 years of age, and this is likely to increase. Surgical patients are more likely to need admission than medical, usually related to sepsis and other postoperative complications. Around 80% of patients over 80 years of age who are ventilated with sepsis do not survive. Other adverse factors include poor cognition, decreased consciousness, recent stroke, limited activities of daily living, poor nutrition and unplanned admission. Despite this, age is a risk factor for poor outcome (7%) by only around one-tenth that of the underlying physiology (73%) in the acute physiology and chronic health evaluation (APACHE) III scoring system. Physiological problems should be much bigger determinants of admission to ITU than age; single-organ reversible disease even in very old people who were previously healthy (another important determinant of outcome) certainly deserves consideration of ITU involvement.

What complications can follow a spell in ITU?

Post-critical illness morbidity is increasingly recognised, particularly in centres operating post-ITU clinics, and this includes neurocognitive dysfunction, neuromuscular dysfunction, disordered taste, a wide variety of neuropathies including peripheral and entrapment neuropathy, tracheostomy site complications, and depression.

CASE 4.32 WITHHOLDING AND WITHDRAWING LIFE-PROLONGING TREATMENTS – ANTIBIOTICS AND DRUGS

Candidate information

Role

You are a doctor on an elderly care ward.

Please read this summary.

Scenario

Re: Mrs Eliza Bennett, aged 83 years

Mrs Eliza Bennett has been on your ward for 3 weeks with unresolving pneumonia. She has significant comorbidity. She has had type 2 diabetes for many years, latterly requiring insulin, with associated chronic kidney disease and advanced diabetic maculopathy. She was admitted with right lower lobe pneumonia, which has failed to respond to two courses of intravenous antibiotics. The microbiologist has suggested a third regimen, but the possibility of non-infective underlying causes, including cancer, is there, although not established, and she has been too unwell for complex investigations. She has steadily declined, with a falling serum albumin and increasing peripheral oedema. She is now too drowsy to engage in discussion. Intravenous access is now not possible peripherally, and your house officer called you to consider a central venous catheter. Mr Bennett is visiting his wife.

Your task is to discuss her treatment options with Mr Bennett, her husband.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Your wife, Mrs Eliza Bennett, is an 83-year-old woman who has been on the ward for 3 weeks with pneumonia that is steadily getting worse. She has been unwell, in your view, for the last year. She has longstanding diabetes, requiring insulin as well as tablets, with associated kidney problems and visual impairment. She used to be very active and has been very depressed for the last year, virtually housebound by weakness in her legs and poor vision. To you, and you think to her, this is the last straw. She is not getting better, her legs are swelling up and you have seen her becoming more confused and drowsy since admission. She has always said that she would not want to go on if her diabetes had got the better of her and would not want to be dependent upon carers or nurses. The doctors are concerned that she has not responded to antibiotics and they appear to be running out of options.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself, establish his identity and acknowledge that it is a difficult time.

2. Acknowledge the value of the relative

As his wife is not able to speak for herself, his presence is highly valuable in determining what her wishes might have been. Acknowledging him as her closest relative, it may be helpful to ask if there are other family members nearby who might also wish to be involved in discussions.

3. Reassure the relative that any decisions will be carefully considered and that the 'burden of responsibility' for difficult decisions will not rest with him

Reassure him that decisions will consider what is best for his wife, and that his views will be very helpful. Explain that you are very concerned that treatments do not seem to be working as you had hoped, and that you now must contemplate what are reasonable interventions and what may not be reasonable interventions and not in his wife's best interests. Explain that decisions will very much take account of any views he has but that decisions will be made together. Remember that your consultant is there to help with difficult decisions such as this, and you should make difficult decisions with more senior team members.

4. Explain the problem

This should start with a summary of the background, explaining that his wife's pneumonia has not responded. Acknowledge that there is uncertainty as to why this is so. It is likely that her diabetes (hyperglycaemia, small-vessel disease, renal failure) is impairing the fight against infection. It may be that there is an underlying reason (including a growth) predisposing to infection, but his wife has been too unwell for more complicated investigations. Explain that, as time goes on, the prospects of recovery from the pneumonia diminish, particularly as other things start to go wrong (drowsiness, hypoalbuminaemia, oedema). Explain that all you have been able to do recently is continue with antibiotics, attempt to correct any abnormalities in the blood chemistry and watch and wait, trying to ensure that she is comfortable. Explain that the new problem is that it is no longer possible to secure peripheral intravenous access for delivery of antibiotics.

5. Explain your view

Explain that the next step could be to consider intravenous access via a catheter inserted into a larger vein in the neck, but that this is more invasive. Acknowledge that this is not without complications, and not always comfortable to insert, but is an effective way of ensuring that treatment continues, although you cannot say if treatment will work. It is unlikely that she is able to take tablets at the moment, but if she were to improve and show the ability to take things orally, then oral antibiotics could be considered.

6. Explore what the relative feels the patient would have wanted

He may request, based on his knowledge of his wife's values and views, that this would be a step too far.

7. Explore any concerns the relative may have

A common concern is that the patient may suffer or be in pain. When a patient is not responding to treatment, it is crucial to reassure relatives that one thing you can do is ensure their comfort.

8. Consider and justify, or plan to change, any apparent discrepancies such as delivering some medications but not others

If a decision is made to withdraw antibiotics, the issue of continuing insulin may need to be discussed. If she cannot take tablets, and is already insulin dependent, then withdrawal of insulin could lead to rapid spiralling of hyperglycaemia and possible death from hyperglycaemic coma. This could be avoided with subcutaneous insulin and this may still be a reasonable intervention while nature confirms its likely course without antibiotics. If and when it becomes certain that she is dying then it may be appropriate to withdraw insulin in favour of purely symptomatic palliative measures.

9. Confirm understanding and invite questions

Make it clear that you are happy to answer further questions now or at any time.

10. Give strong reassurance about continuing with care

Make it clear that the team will continue to care for his wife with very close attention to what is reasonably treatable and to alleviation of symptoms. Tell him that you are happy to answer questions at any time.

Discussion

Do you know of any guidance on withholding and withdrawing life-prolonging treatments?

The 2010 General Medical Council (GMC) guideline on end-of-life care supersedes previous guidance on withholding and withdrawing life-prolonging treatment and covers greater ground, providing decision-making models (Case 4.27 End of life and palliative care) for patients with or without capacity in all areas of end-of-life care including withholding and withdrawing life-prolonging treatments.

Must you provide treatment to a patient who demands it but which you do not think is in that patient's best interests?

If a patient asks for a treatment that the doctor considers not clinically appropriate, the doctor is not obliged to provide it, but should offer to arrange for a second opinion.

How might you be guided in making decisions about limitation of treatment for patients without capacity?

Any valid advance refusal of treatment must be respected. Without this, assessment of the benefits, burdens and risks and overall acceptability of treatment must be made on a patient's behalf by the doctor, taking into account what is known of the patient and information from those closest to the patient. Best-interests decisions and the use of valid advance decisions or legal proxy or information from third parties are described in more detail in Case 4.24 (Consent and capacity).

Prolonging life will usually be in a patient's best interests if treatment is not excessively burdensome or disproportionate to expected benefits.

But not continuing or starting treatment is in a patient's best interests when there is no net benefit. Life has a natural end and doctors should not strive to prolong the dying process. Case law suggests that life-prolonging treatment can lawfully be withheld or withdrawn from a patient who lacks capacity when starting or continuing treatment is not in their best interests, and that there is no obligation to give treatment that is futile or burdensome. When reaching a view on whether a particular treatment would be more burdensome than beneficial, assessments of the likely quality of life for the patient with or without that treatment may be one of the appropriate considerations. Where it is decided that treatment is not in a patient's best interests, there is no ethical or legal reason to provide it and thus no need to distinguish withdrawal of treatment from not starting treatment.

Where a patient lacks capacity and there is uncertainty about appropriateness of treatment, treatment that may be of some benefit should be started until clearer assessment is made. This is particularly important in emergencies where there may be doubt about the severity of a condition or the benefit of a treatment.

CASE 4.33 WITHHOLDING AND WITHDRAWING LIFE-PROLONGING TREATMENTS – CLINICALLY ASSISTED NUTRITION AND HYDRATION

Candidate information

Role

You are a doctor on the stroke unit.

Please read this summary.

Scenario

Re: Mr Harold Hunt, aged 86 years

Mr Hunt was admitted to your ward 3 days ago following a left total anterior circulation stroke. He remains unconscious and the consensus opinion of all members of the health-care team is that his prognosis is very poor. His daughter feels that he should be 'left in peace'. He is on 'a drip' but one of the nurses mentioned the possibility of a 'feeding tube' to her. She is now not sure if he is being starved.

Your task is to discuss the issue of clinically assisted nutrition and hydration with his daughter.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Harold Hunt, your father, is an 86-year-old man who was admitted to the ward 3 days ago following a very large stroke. He remains unconscious and the consensus opinion of all members of the health-care team is that his prognosis is very poor. You feel that he should be 'left in peace'. He had a very active life in the army, but since being widowed 3 years ago became rather withdrawn and always said he would want 'to have all of his faculties'. He has been on 'a drip' since admission but one of the nurses mentioned the possibility of a 'feeding tube'. You do not see the value of feeding your father if he is going to die, but are worried that if he is being starved it may be uncomfortable for him. You wonder if the drip should continue, and if so whether it might be delaying an inevitable death.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself, establish her identity and acknowledge that it is a difficult time.

2. Acknowledge the value of the relative

As her father is not able to speak for himself, her presence is highly valuable in determining what his wishes might have been. It is always useful to establish if there are other people who might wish to be involved in discussions.

3. Reassure the relative that any decisions will be carefully considered and that the 'burden of responsibility' for difficult decisions will not rest with her

Reassure her that decisions will always consider her father's best interests first, aided by her better knowledge of her father. Although relatives often wish strong account be taken of their views, they may also need to be reassured that ultimately the 'burden of responsibility' for decisions rests with the medical team. She will wish to express the perceived values and preferences of her father but may well feel uncomfortable if she feels that a life and death decision about a family member is hers.

4. Explain the reasons for and against clinically assisted nutrition and hydration

Explain that where a patient cannot take fluids or food orally, an assessment is always made of the requirements for hydration and nutrition, and the appropriateness of instituting these. Explain that in this situation intravenous fluids were started initially because it could not be determined whether her father would recover and, if so, how long this would take, but that supportive fluids are necessary early on if there is to be some recovery. Explain that artificial nutrition is less immediate, but should be started via a tube passed through the nose directly into the stomach (nasogastric tube) within the first few days in patients showing signs of recovery. Acknowledge that it is a very sensitive issue and not one with absolutely right or wrong answers, but that the generally accepted view is not to institute artificial nutrition unless a patient is showing signs of recovery. Specifically, a patient should be conscious and able to sit up and ideally aware of the reasons for the tube.

5. Explain your view

It is often best, particularly where you feel relatives are showing agreement, to suggest what you think might be appropriate, provided this is not dogmatic and you demonstrate willingness to be fluid in your decisions depending upon feedback. You might consider artificial nutrition if there were a spontaneous change for the better, but now it is entirely reasonable to watch and wait.

6. Explore what the relative feels the patient would have wanted

She will probably agree with withholding nutrition.

7. Explore any concerns the relative may have

She may need to be reassured that there is no evidence that withholding nutrition causes distress by 'starvation'. She may not see the logic of maintaining intravenous fluids when nutrition is being withheld.

8. Consider and justify or plan to change any apparent discrepancies such as delivering hydration but withholding nutrition

The British Medical Association (BMA) and General Medical Council (GMC) have stated that withdrawing a life-prolonging treatment may not be ethically distinguishable from withholding it, although the former can seem more difficult. Whilst intravenous or subcutaneous fluids could be withdrawn, there are reasons for continuing their provision, although these cannot be evidence based. In this case 3 days may seem too soon to withdraw a relatively non-invasive treatment, especially if access for fluids is not causing distress. Unlike nutrition, fluids pose little risk. Nasogastric feeding may provoke aspiration and may be uncomfortable and is not suitable for unconscious or agitated patients or for patients who cannot sit up. Percutaneous endoscopic gastrostomy (PEG) feeding is not suitable unless patients demonstrate potential for longer term survival. Hydration may avert distress, although there is no convincing evidence for this and indeed the Liverpool Care Pathway for palliation specifically excludes hydration and nutrition.

9. Confirm understanding and invite questions

Make it clear that you are happy to answer further questions now or at any time.

10. Give strong reassurance about continuing with care

Explain that needs and symptoms may change, and that he will be carefully assessed regularly.

Discussion

When might the question of clinically assisted nutrition or hydration be considered?

The offer of food and drink by mouth is part of basic care (as is the offer of washing and pain relief) and must always be offered to patients able to swallow without serious risk of choking or aspirating. Food and drink can be refused by patients at the time it is offered, but an advance refusal of food and drink has no force. If a patient is not receiving adequate nutrition or hydration by mouth, even with support, an assessment of their condition and their individual requirements must be made. Their needs for nutrition and hydration must be considered separately with consideration of what forms of clinically assisted nutrition or hydration may be required.

What is meant by clinically assisted nutrition or hydration?

Clinically assisted nutrition includes intravenous feeding, and feeding by nasogastric tube and by PEG and radiologically inserted gastrostomy feeding tubes through the abdominal wall. All these means of providing nutrition also provide fluids necessary to keep patients hydrated. Clinically assisted hydration can also be provided by intravenous or subcutaneous infusion of fluids through a ‘drip’. The terms ‘clinically assisted nutrition’ and ‘clinically assisted hydration’ do not refer to help given to patients to eat or drink, for example by spoon feeding – these are generally considered part of nursing care. The terms are replacing the term ‘artificial hydration’ and ‘artificial nutrition’.

How might you decide if clinically assisted nutrition or hydration should be provided?

Providing nutrition and hydration by tube or drip may provide symptom relief, or prolong or improve quality of life, but may also present problems, and decision-making models should be used to help determine whether these should be provided (Boxes 4.23 and 4.29).

Should clinically assisted nutrition or hydration should be provided in advanced dementia?

An increasingly common scenario is advanced dementia, when poor oral intake is a result of irreversible brain failure resulting in loss of motivation for intake with apathy, and sometimes to an extent a weak swallow. Here it is usually appropriate to exclude reversible factors, including depression, and encourage oral intake with all possible means, which can be time intensive. If clear that the patient is declining primarily because of the dementia and that the poor oral intake is a consequence of this, the benefits of clinically assisted hydration and nutrition become less and less persuasive and are not without considerable burdens and risks. Ultimately, the ethical distinction between allowing a patient to decline or die primarily from dehydration (usually unethical) or accepting decline and death primarily from an underlying irreversible disease in which dehydration is a secondary inevitable factor (which may be ethical) is an important one. Furthermore, in advanced dementia the risks of artificial feeding are higher than the benefits, invariably, and the point is that food and fluid are not withheld but always offered orally.

A 68-year-old man with advanced Lewy body dementia is admitted with an unsafe swallow and multiple failed nasogastric feeding attempts because he pulls out the tubes. He is receiving intravenous fluid. His essential medical therapy is warfarin for a metallic heart valve. What are the options?

Percutaneous gastrostomy feeding would probably not be appropriate in this situation. Blood tests are appropriate to guide a life-saving treatment (warfarin) until a definitive decision for no further active management has been made. The option to comfort feed may seem the most appropriate to medical staff, but his family’s views on his perceived wishes may help. Withdrawal of hydration before discussion would not seem correct immediately, particularly while his family are coming to terms with a difficult situation. His family are likely to be strongly in agreement that no further attempts should be made to feed via a nasogastric tube. It may be decided that if no future can be envisaged beyond this admission to hospital, no further intravenous or subcutaneous access for hydration would be appropriate once the current cannula ‘tissues’. A decision should then also be made as to whether or not to give antibiotics in the event of aspiration. Assurance of preservation

Box 4.29 Deciding if clinically assisted nutrition or hydration should be provided

If clinically assisted nutrition or hydration is necessary to keep a patient alive, the duty of care will normally require the doctor to provide it, if a patient with capacity wishes to receive it. But the evidence about the benefits, burdens and risks of these techniques as patients approach the end of life is not straightforward and clear. This can lead to concerns that patients who are unconscious or semi-conscious may be experiencing distressing symptoms and complications, or otherwise be suffering either because their needs for nutrition or hydration are not being met or because attempts to meet their perceived needs for nutrition or hydration may be causing them avoidable suffering. Clinically assisted nutrition or hydration may be withheld or withdrawn if the patient does not wish to receive it, or if the patient is dying and the care goals change to palliative care and relief of suffering, or if the patient lacks capacity to decide and it is considered that providing clinically assisted nutrition or hydration would not be in their best interests.

Nutrition and hydration provided by tube or drip are regarded in law as medical treatment and should be treated in the same way as other medical interventions. Nonetheless, some people see nutrition and hydration, whether taken orally or by tube or drip, as part of basic nurture for the patient that should almost always be provided. For this reason it is especially important to listen to and consider the views of the patient and of those close to them (including their cultural and religious views) and explain the issues, including the benefits, burdens and risks of providing clinically assisted nutrition and hydration. All should understand that when clinically assisted nutrition or hydration would be of overall benefit it will always be offered, and that if a decision is taken not to provide clinically assisted nutrition or hydration the patient will continue to receive high-quality care, with any symptoms addressed.

Patients who have capacity

If it is considered that a patient is not receiving adequate nutrition or hydration by mouth, the decision model in Case 4.27 should be followed. Nutrition and hydration should be considered separately and considered clinically appropriate because, for example, they would provide symptom relief or are likely to prolong life. Benefits, burdens and risks should be explained. If clinically assisted nutrition or hydration is not considered clinically appropriate the patient's condition should be monitored and the benefits, burdens and risks reassessed as the condition changes. If a patient asks for nutrition or hydration by tube or drip, the reasons for their request should be explored, giving weight to the patient's wishes and values. When the benefits, burdens and risks are finely balanced, the patient's request will usually be the deciding factor. However, if after discussion the treatment is still not considered clinically appropriate, it does not have to be provided, but the reasons and other options should be explained, including the option to seek a second opinion.

Adult patients who lack capacity

If a patient lacks capacity and cannot eat or drink enough to meet their nutrition or hydration needs, assessment of whether providing clinically assisted nutrition or hydration would be of overall benefit should be made using the decision model in Case 4.27 (End of life and palliative care) with the same clinical considerations as for patients who have capacity.

Adult patients who lack capacity and are not expected to die within hours or days

Clinically assisted nutrition or hydration must be provided if it would be of overall benefit, taking into account the patient's beliefs and values, any previous request for nutrition or hydration by tube or drip and any other views he or she has previously expressed about care. The patient's request must be given weight and, when the benefits, burdens and risks are finely balanced, will usually be the deciding factor. If judged that the provision of clinically assisted nutrition or hydration would not be of overall benefit to the patient, it may be concluded that treatment should not be started or should be withdrawn. This view should be explained to the patient, if appropriate, and those close to the patient, and the patient's interests must have been thoroughly considered including where appropriate steps to get a second opinion from a senior clinician with experience of the condition but not directly involved in the patient's care. If consensus is reached that clinically assisted nutrition or hydration would not be of overall benefit treatment is withdrawn or not started, and the patient must be kept comfortable and monitored for any change with preparedness to reassess the benefits, burdens and risks of providing clinically assisted nutrition or hydration in light of changes. If clinically assisted nutrition or hydration is started or re-instated after a later assessment, and it is subsequently concluded that it would not be of overall benefit to continue a further second opinion should be sought.

Adult patients who lack capacity and are expected to die within hours or days

If a patient is expected to die within hours or days, and it is considered that the burdens of providing clinically assisted nutrition or hydration outweigh the benefits they are likely to bring, it will not usually be appropriate to start or continue treatment (it is important to be aware that not eating and drinking is often a part of the dying process and should be distinguished from dying as a result of not receiving food or fluid). If a patient has previously requested that nutrition or hydration be provided until death, or those close to the patient are sure that this is what the patient wanted, the patient's wishes must be given weight and, when the benefits, burdens and risks are finely balanced, will usually be the deciding factor.

Patients in a persistent vegetative state (PVS) or similar condition

If considering withdrawing nutrition or hydration from a patient in a PVS or a condition closely resembling PVS, the courts in England, Wales and Northern Ireland currently require that they be approached for a ruling. The courts in Scotland have not specified such a requirement, but legal advice should be sought.

of his dignity should be given, with a shift in care to comfort and suppression of distress. Warfarin should be withdrawn as blood tests cannot be obtained, and the possibility of sudden valve obstruction accepted as a potential mode of death unless he is not likely to die from other causes quickly in which case subcutaneous heparin could be administered after discussion with his family.

He shows signs of improvement with comfort feeding but has choking episodes with comfort feeding. What would you do now?

There are two, at first glance conflicting, options but each one depends upon the type of improvement. If he is showing signs of returning to his pre-admission self, then it may well be appropriate to revise decisions, and this could include stopping comfort feeding, administering artificial hydration and considering percutaneous gastrostomy feeding, although there are enormous concerns about the risk–benefit ratio of the latter in dementia. If, however, he shows the day-to-day minor undulation that is true of many hospital patients, then it is vital for his family not to be given false hope or to burden the patient or family with swinging decisions in the context of an inevitable end.

CASE 4.34 PERCUTANEOUS ENDOSCOPIC GASTROSTOMY FEEDING

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr James Hawkins, aged 82 years

Mr Hawkins was admitted to your ward a week ago with aspiration pneumonia. On admission the prognosis seemed poor and resuscitation in the event of cardiac or respiratory arrest was not considered appropriate. He has idiopathic epilepsy (since childhood, and currently treated with phenytoin, carbamazepine and sodium valproate) and Parkinson's disease, on treatment for 8 years. A year ago he had a stroke after which he spent 6 weeks in a rehabilitation hospital before returning to his wife at home. She is his main carer, and he requires help with washing, dressing, meals and mobility around the house. Following antibiotic treatment he has recovered to the point of cardiorespiratory stability, but cannot swallow. The speech and language therapist assessing him believes he might never safely swallow because this was significantly impaired before admission and the balance has now been tipped. Unfortunately, Mr Hawkins has not tolerated numerous attempts to pass a nasogastric feeding tube and the speech and language therapist has suggested that a percutaneous endoscopic gastrostomy (PEG) would enable him to receive nutrition. Unfortunately, Mr Hawkins is unable to participate in such a discussion because he has been too cognitively impaired for the last year. His wife fears that he will starve without a PEG and wishes to discuss the issues with you.

Your task is to discuss the options with her and help her reach a decision.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr James Hawkins, your husband, is an 82-year-old man admitted to hospital a week ago with aspiration pneumonia. On admission the prognosis seemed poor and resuscitation in the event of cardiac or respiratory arrest was not considered appropriate. He has epilepsy (on treatment since childhood) and Parkinson's disease (on treatment for 8 years). A year ago he had a stroke after which he spent 6 weeks in a rehabilitation hospital before returning home. You are his main carer, and he requires help with washing, dressing, meals and moving around the house. He is confined to a wheelchair much of the time, but sometimes can walk with a stick. Following antibiotic treatment he has recovered somewhat, but cannot swallow. The speech and language therapist believes he might never safely swallow again. Unfortunately, he has not tolerated numerous attempts to pass a nasogastric feeding tube and the speech and language therapist has suggested that a percutaneous endoscopic gastrostomy (PEG) feeding tube would enable him to receive nutrition. Unfortunately, he is unable to participate in such a discussion because he has been too cognitively impaired for the last year. You fear that he will ultimately starve without a tube and will not receive his usual medications, and wish to discuss the issues with the doctor.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself, confirm her identity and say that you would like to respond to her concerns about feeding and discuss possible ways to tackle this.

2. Explain the current situation as you see it

Explain that, despite some improvement, the position remains very serious. Explain the reasons for considering a PEG tube, in this case delivery of medications and administration of feeding.

3. Explain the main issues relating to PEG tubes

Discuss the issues relevant to PEG tube insertion in more detail. Explain that it might not be a means of improving or prolonging life. Explain there is no good evidence that it would do so where there are problems with memory and understanding. There would be a small but significant risk of complications including peritonitis (around 2%) and an increased risk of aspiration, which in this case is particularly relevant.

4. Try to establish the patient's wishes

Ask if she and her husband have ever discussed what his wishes might be if such a scenario ever arose.

5. *Explain alternatives*

Explain that the alternative is to administer medications via alternative routes (phenytoin intravenously, diazepam rectally), but that not all drugs can be delivered, and for practical purposes there would be no feeding and so inevitably there would be a starvation factor. Point out that fluids can be given intravenously or subcutaneously (a small needle under the skin of the abdomen).

6. *Be alert to cues*

Do not simply deliver your spiel without being aware of any reactions she may have.

7. *Explore her concerns*

Understand that it is a heart-rending decision. Ask if she has any particular feelings about things at this stage. Explain that a decision does not have to be made now. Patients' and relatives' expectations from PEG tube feeding are often improved nutrition, prevention of aspiration, extension of life, improvement of pressure sores, comfort, strength and help in overcoming an acute illness. The evidence is that rarely do patients achieve these expectations; in 70% there may be no improvement and there is no prevention of aspiration; in the frail elderly there is a 30-day mortality of 22% and a 1-year mortality of 50%.

8. *Respond to questions*

She might ask for your advice. You might say that putting everything together, without seeing a clear way forward to long-term improvement, it may not be in his best interests to 'go there'. If that is what she decides then assure her that there is no evidence that he would suffer from things like hunger pains, not at this stage.

9. *Confirm understanding and agree a way forward*

Make sure that she has enough information and either agree a way forward or allow her more time to think things over.

10. *Reassure that decisions are not irreversible*

Make it clear that no decision that she or the medical team makes is irreversible and of course if the situation were to change then any decision could be reviewed.

Discussion

A 68-year-old man has a left total anterior circulation stroke with right hemiparesis and dysphagia. His swallow is deemed unsafe by the speech and language therapy (SLT) team. His family want to know if you will be feeding him to keep his strength up. When is enteral feeding recommended and what methods are there?

Enteral feeding in adult hospital patients is indicated if feeding is likely to be delayed more than 5–7 days. Earlier instigation is favoured in malnourished patients. Methods for enteral feeding are nasogastric tube (NGT) feeding, PEG or less commonly percutaneous endoscopic jejunostomy feeding.

At day 2 the SLT team feel his swallow is still unsafe and NGT feeding is suggested. What are the complications of NGT insertion?

These include discomfort, epistaxis, oesophageal stenosis, aspiration and complications from enteral feeds.

At day 10 the SLT team feel his swallow has shown little sign of improvement. A gastrostomy tube is recommended. What do you know about gastrostomy feeding?

A gastrostomy tube is considered when nutritional intake is likely to be impaired for more than a few weeks or when a NGT is not tolerated or is contraindicated. PEG feeding is an effective way of providing enteral feeding to patients who have functionally normal gastrointestinal tracts but who cannot meet their nutritional needs because of inadequate oral intake. The procedure places a feeding tube directly into the stomach via a small incision through the abdominal wall and utilises a powerful light source from an endoscope and insufflation of air to allow positioning.

What are the benefits of gastrostomy feeding?

Malnutrition determines disease outcomes because it affects every system in the body, leading to both physical and psychological disability. PEG feeding aims to improve nutritional status and reduces mortality, length of hospital stay and complications in carefully selected patients who are likely to be or later become nutritionally depleted for longer than 4–6 weeks. Studies have shown clear benefits of PEG feeding after stroke (in terms of improving nutritional status and reducing mortality) and in patients with oropharyngeal cancer (in terms of improving nutritional status). When compared with other methods of enteral nutrition, such as NGT feeding, gastrostomy feeding caused less discomfort and had lower rates of complications such as bleeding, blockage and dislodgment of the tube, and possibly lower rates of reflux and aspiration although these may still occur.

Which patients may be considered for gastrostomy feeding?

Although studies have shown benefits for PEG feeding in stroke and oropharyngeal cancer, the appropriateness of gastrostomy insertion in other patient subgroups is controversial. Other conditions for which patients are commonly referred for PEG tube insertion include motor neurone disease, multiple sclerosis, Parkinson's disease, dementia, head injury, intensive care patients, oropharyngeal cancer and oesophageal cancer. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) undertook the largest study in the UK of mortality after PEG insertion and found a 6% mortality in a cohort of 16 648 patients. Of those who died, 43% died within 1 week of PEG insertion, and in 19% of patients PEG insertion was thought to have been futile. Each patient must be considered according to his or her individual needs.

What are the contraindications to gastrostomy?

Active coagulopathies and thrombocytopenia must be corrected. Anything that precludes endoscopy, such as haemodynamic compromise, sepsis or a perforated viscus, is an absolute contraindication.

What are the complications of gastrostomy feeding?

These may be immediate, early or late:

- Immediate (< 72 hours) – endoscopy related, haemorrhage or perforation, aspiration, oversedation
- Early – ileus, pneumoperitoneum, wound infection, wound bleeding, trauma
- Delayed – gastric outlet obstruction, buried bumper syndrome, dislodged tube, peritonitis, peristomal leakage or infection, skin or gastric ulceration, blocked tube, tube degradation, gastric fistula after removal of tube, granulation around site of insertion.

Overly granulated stoma sites are common. Treating the cause, such as gastric leakage, infection or poor position, may be more appropriate than the non-evidence-based measures to treat. Blockage is usually secondary to drugs or feed. It can sometimes be removed by massaging the tube, or a push–pull method using a syringe on the end, or enzyme preparations or fizzy drinks may be delivered into the tube. Inadvertent removal occasionally occurs, and delay in recognising may result in stoma closure; a urinary catheter may be used as a holding measure to prevent closure. Feed-related peritonitis is possible after reinsertion of a gastrostomy tube. When uncertainty exists about the position of a replacement tube, water-soluble contrast can determine position before feeding is re-started. The 'buried bumper' syndrome is rare but serious – the internal bumper migrates from the gastric wall towards the skin, anywhere along the PEG tract, as a consequence of excessive tension between the internal and external bumper. Symptoms may include pain on feeding, retrograde leakage of feed onto skin, and rarely gastric perforation.

What is the role of gastrostomy feeding in dementia?

There is insufficient evidence to support PEG feeding in dementia and other neurodegenerative diseases. Patients with advanced dementia develop feeding problems from lack of motivation and sometimes impaired swallow. Whether or not to use percutaneous gastrostomies to feed patients with dementia is an emotive and controversial question, compounded by the fact that patients often lack capacity. A Cochrane review showed no evidence of increased survival, reduced pressure ulcers or improved quality of life, nutritional status, function, behaviour or psychiatric symptoms of dementia in patients with advanced dementia fed with gastrostomy tubes. No large prospective studies have examined outcomes of PEG feeding in patients with dementia. A retrospective study of 361 patients found that patients with dementia who had a PEG inserted had higher mortality than other patient subgroups (54% 30-day mortality and 90% at 1 year). These findings have been reproduced by other investigators, who found that eating problems occurred in 85.8% of patients with dementia before death, which suggests that difficulties with feeding are an end-stage problem. Guidelines on dementia highlight the importance of quality of life in advanced dementia and support the role of palliative care in these patients from diagnosis until death. Best practice in these patients could be to encourage eating and drinking by mouth for as long as tolerated, to use good feeding techniques, to alter the consistencies of food, and to promote good mouth care. When disease progression is such that the patient no longer wants to eat or drink, then rather than inserting a gastrostomy tube end-of-life care pathways might be considered.

What is re-feeding syndrome?

Re-feeding syndrome refers to potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving rapid enteral or parenteral nutrition. The syndrome is due to metabolic and hormonal changes. The hallmark is hypophosphataemia, but the syndrome is complex and may include hypokalaemia, hypomagnesaemia, thiamine deficiency and changes in sodium and fluid balance, changes in calcium, and changes in glucose, fat and protein metabolism.

Normal glucose metabolism

Glycolysis normally converts glucose to pyruvate via a series of oxidation reactions and enzymes including pyruvate kinase to produce ATP/energy (Fig. 4.1). Excess glucose is converted to glycogen for storage via glycogenesis. During strenuous exercise glycogenolysis and glycolysis produce more energy, but if the rate of these processes exceeds oxygen delivery then anaerobic glycolytic pathways are used, which generate lactate.

Starvation

In early starvation the body switches from carbohydrate to protein and fat metabolism. The glucose needed to produce energy from glycolysis is generated from two mechanisms; both of these gluconeogenesis mechanisms occur chiefly in the liver (Fig. 4.1):

- Lipolysis, which converts triglycerides in adipose tissue to fatty acids and glycerol, the latter convertible to glucose

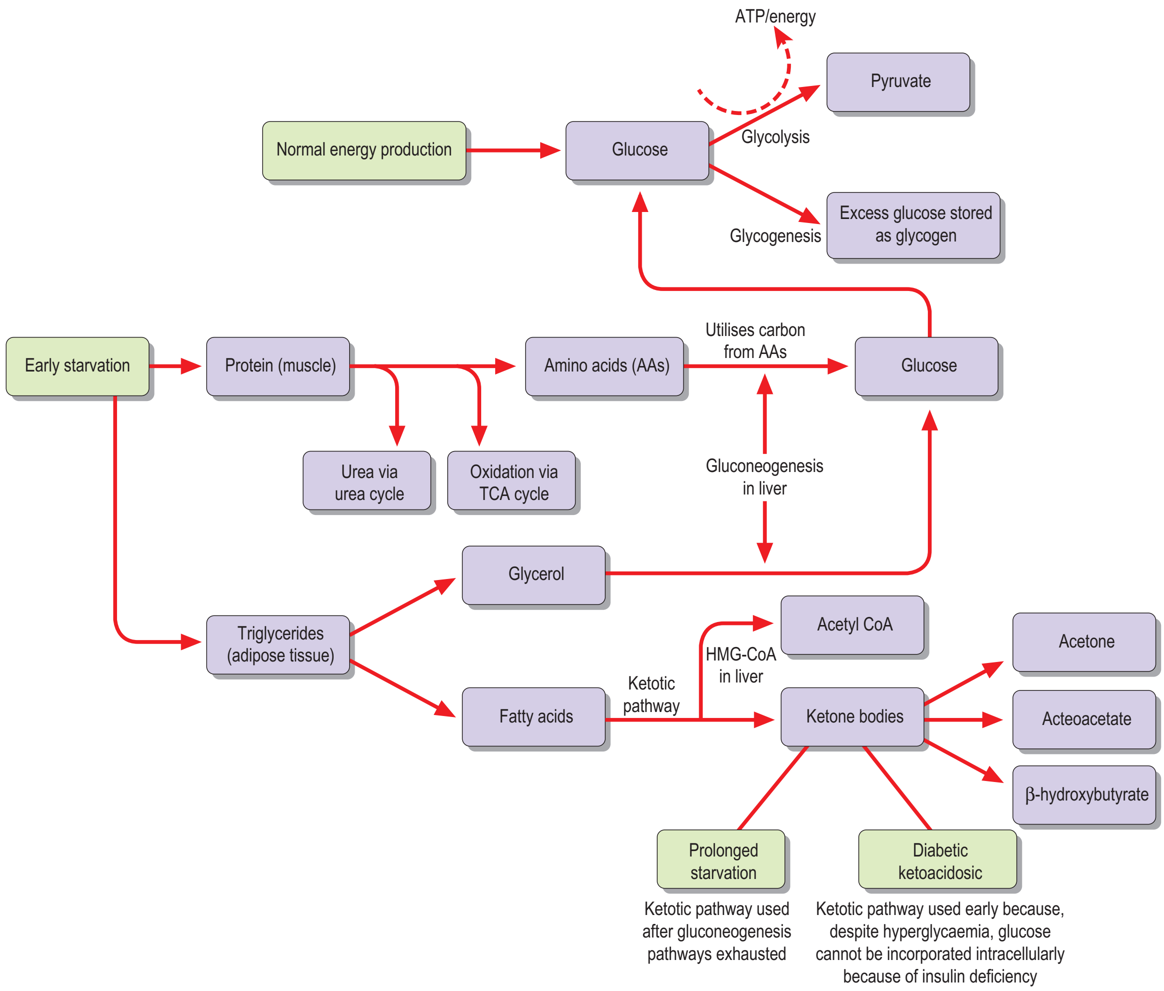
ATP/energy
Pyruvate
Normal energy production
Glucose
Glycolysis
Excess glucose stored as glycogen
Glycogenesis
Utilises carbon from AAs
Early starvation
Protein (muscle)
Amino acids (AAs)
Glucose
Urea via urea cycle
Oxidation via TCA cycle
Gluconeogenesis in liver
Glycerol
Acetyl CoA
HMG-CoA in liver
Acetone
Triglycerides (adipose tissue)
Ketotic pathway
Fatty acids
Ketone bodies
Acteoacetate
β-hydroxybutyrate
Prolonged starvation
Diabetic ketoacidosic
Ketotic pathway used after gluconeogenesis pathways exhausted
Ketotic pathway used early because, despite hyperglycaemia, glucose cannot be incorporated intracellularly because of insulin deficiency

Figure 4.1 Glucose metabolism, starvation and diabetic ketoacidosis. ATP, adenosine triphosphate; CoA, coenzyme A; HMG, 3-hydroxy-3-methylglutaryl; TCA, tricarboxylic acid cycle..

- Protein catabolism, in which protein, largely from muscle, is degraded to amino acids and the carbon from amino acids is subsequently used in glucose synthesis; starvation is a highly catabolic state, and urea is produced reflecting this.

In prolonged starvation, metabolic and hormonal changes aim to prevent muscle and protein breakdown, and the liver reduces its rate of gluconeogenesis to preserve muscle. Now, the ketotic pathway (Fig. 4.1) in which fatty acids are used to produce ketone bodies, an alternative source of fuel for most cells, is prominent. The brain, generally unhappy to use ketones for energy, may be forced to do so in more desperate starvation states. During prolonged starvation, some electrolytes such as phosphate are severely depleted, although serum levels may remain normal since these electrolytes are mainly in the intracellular compartment, which contracts in starvation, and renal excretion is reduced.

Diabetic ketoacidosis (DKA) similarities to starvation

The ketotic pathway in DKA is the same as that used in starvation (Fig. 4.1), but it occurs earlier and is more severe. In starvation insulin levels fall in response to the lack of food and glucose. In DKA insulin levels are low owing to insufficient production leading to hyperglycaemia; however, intracellular glucose levels are very low because without insulin glucose cannot be taken up by cells, and alternatives to glycolysis for energy production must be sought immediately.

Re-feeding

Glycaemia in re-feeding increases insulin and decreases glucagon secretion, stimulating glycogen, fat and protein synthesis, a process requiring phosphate, magnesium and thiamine, and driving potassium and glucose into cells through an ATPase sodium–potassium pump; phosphate and magnesium are also taken up into cells. The clinical manifestations of re-feeding syndrome result from these depleted electrolytes and the sudden increase in metabolic rate.

Clinical manifestations of re-feeding syndrome

These are outlined in Table 4.6.

How may re-feeding syndrome be prevented and managed?

An individualised re-feeding regimen should be determined by a dietitian to prevent re-feeding syndrome (Box 4.30).

Where phosphate is moderately (0.3–0.6 mmol / l) or severely (< 0.3 mmol / l) depleted, an intravenous infusion of 9 mmol or 18 mmol, respectively, should be delivered over 12 hours. Where magnesium is moderately depleted (0.5–0.7 mmol / l), intravenous replacement should be 0.5 mmol / kg / day over 24 hours then 0.25 mmol / kg / day for 5 days; where magnesium is severely deplete (< 0.5 mmol / l), intravenous replacement should be 24 mmol over 6 hours then as for moderately depleted.

Table 4.6 Clinical manifestations of re-feeding syndrome

Deficiency	Clinical manifestations
Phosphate	Widespread cellular dysfunction of most physiological processes
Potassium	Cardiac arrhythmias
Magnesium	Cardiac and neuromuscular instability
Thiamine	Wernicke's encephalopathy (ocular abnormalities, ataxia, confusion, hypothermia, coma) Korsakoff's syndrome
Sodium and water	Fluid overload (rapid introduction of glucose after starvation reduces urine output)

Box 4.30 **Prevention of re-feeding sydrome**

- Check potassium, calcium, phosphate and magnesium
- Prior to feeding administer thiamine 200–300 mg daily orally, one or two high-potency vitamin B tablets thrice daily (or intravenous vitamin B), and multivitamin or trace element supplements daily
- Start feeding slowly (no more than 50% of energy requirements to start with, 0.0418 MJ/kg / day, slowly increasing over 4–7 days)
- Ensure adequate hydration
- Supplement and / or correct any levels of potassium (2–4 mmol / kg / day), phosphate (0.3–0.6 mmol / kg / day), calcium and magnesium (0.2 mmol / kg / day intravenously or 0.4 mmol / kg / day orally) and monitor and amend treatment for these electrolytes for 2 weeks

CASE 4.35 VEGETATIVE STATE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Roger Hunt, aged 19 years

Mr Hunt is a 19-year-old patient with type 1 diabetes who sustained severe cortical brain damage from an episode of prolonged hypoglycaemia while out drinking with friends at New Year. He breathes spontaneously but has been on your ward for 4 months and not shown any signs of interacting with his environment. He receives percutaneous gastrostomy feeding. He has had two episodes of aspiration pneumonia. His father is convinced he will get better one day, but is concerned that the doctors will label his son as being in a persistent vegetative state and seeks your reassurance that you will not stop actively treating future infections or providing artificial hydration and nutrition.

Your task is to address his father's concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient / subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient / subject. You are not required to examine the patient / subject.

Patient / subject information

Your son, Roger Hunt, is 19 years old and has type 1 diabetes. Four months ago he sustained severe brain damage from an episode of prolonged hypoglycaemia while out drinking with friends. He breathes spontaneously but, according to the doctors, has not shown any signs of interacting with his environment. However, you are certain that he occasionally smiles and even seems to shed tears in your and your wife's company. He receives percutaneous gastrostomy feeding. He has had two episodes of pneumonia. You are convinced he will get better one day, but are very concerned that the doctors will label him as being in a persistent vegetative state. You want reassurance that the doctors will not stop actively treating future infections or providing artificial hydration and nutrition.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish that he is Mr Hunt's father.

2. Establish what the relative knows

Firstly, establish what he knows about his son's condition, so that you have a basis for addressing his concerns.

3. Elicit ideas, concerns and expectations

Explore his ideas, concerns and expectations, actively listening.

4. Address ideas, concerns and expectations

Start with an immediate reassurance that there are no plans to withdraw care for his son. Note his remark about a persistent vegetative state. Explain that at this stage in his son's illness there would be every attempt to vigorously treat any infection, manage his diabetes carefully and of course provide full hydration and nutrition in conjunction with appropriate colleagues. Explain that certain movements and facial gestures are not uncommon in this situation, and that while you do not have the expertise to be sure that they are not signs of awareness, your understanding is that they could very well be involuntary reflex movements. The point is that you do not want to unequivocally remove hope and yet you want to truthfully reinforce what seems likely.

5. Be alert to cues

Throughout your explanation, be alert and ready to address any cues suggesting concern or disagreement. Above all, be empathetic and at no point challenge his desire to see his son get better, even though you may be less certain of its likelihood.

6. Elaborate on the meaning of the term persistent vegetative state

Offer to explain more about a persistent vegetative state. In particular explain that a diagnosis cannot be made this early on in the illness and can only be made later by certain specialists.

7. Be honest about the prognosis as it appears now

At the same time, do not reinforce what you feel to be excessive hope. Explain that you and the medical and nursing team would have hoped that more definite signs of improvement would have started to develop by now, and that as time goes on the prospects of the recovery that you would all wish for become less easy to envisage.

8. Concede uncertainty

Despite this, concede that at this stage there are no certainties; that alone is often a heart-rending thing to wrestle with.

9. Invite questions

Make sure there are no areas that have not been discussed and express that you are willing to address any issues at any time with him.

10. Conclude with assurances

Reiterate that at this stage a diagnosis of persistent vegetative state has not and cannot be made, and that you will continue to actively treat his son's condition and any complications.

Discussion

What is the vegetative state?

The vegetative state is a complex neurological condition in which patients appear awake but show no sign of awareness of themselves or their environment. It may develop suddenly (as a consequence of traumatic or non-traumatic brain injury, such as hypoxia, infection or haemorrhage) or gradually (in the course of a neurodegenerative disorder, such as Alzheimer's disease). It is uncommon, and appears perplexing because there is apparent dissociation between the two cardinal elements of consciousness: awareness and wakefulness. Guidance produced by the Royal College of Physicians in 2003 defines it as 'a clinical condition of unawareness of self and environment in which the patient breathes spontaneously, has a stable circulation, and shows cycles of eye closure and opening which may simulate sleep and waking.' Thus three main clinical features define the vegetative state (Box 4.31).

Since the brain damage is cortical and the brainstem is preserved, awareness and consciousness are lost but breathing and circulation are spontaneous and support in an intensive care unit is not usually required. Patients may experience sleep–wake cycles or be in a state of chronic wakefulness. Wakefulness is determined by nuclei in the

Box 4.31 **The three features of the vegetative state**

1. Cycles of eye opening and closing, giving the appearance of sleep–wake cycles (whether this reflects the circadian rhythms is unclear)
2. Complete lack of awareness of the self or the environment
3. Complete or partial preservation of hypothalamic and brainstem autonomic functions

Royal College of Physicians guidelines consider a vegetative state persistent when longer than a month and permanent when longer than 6 months for non-traumatic brain injuries (3 months in US guidelines) and 1 year for traumatic brain injuries. Persistent and permanent vegetative states are often abbreviated to 'PVS'.

hypothalamus that coordinate the circadian rhythm and is a prerequisite for consciousness and awareness, but in the event that higher centres (the cerebral cortex) are severely damaged or destroyed the wakefulness is without consciousness or awareness. Apparent awareness in this state of wakefulness, including opening of eyes, movements, swallowing and even emotional outbursts, are automatic reflexes. Spontaneous eye opening indicates intact brainstem arousal mechanisms but not necessarily awareness.

How does the vegetative state differ from other disorders of consciousness such as coma?

Experts suggest that the vegetative state should be seen as part of a continuous spectrum of disorders of consciousness, in which someone's wakefulness and/or awareness are impaired after severe brain injury (Table 4.7).

What is coma?

Coma is a condition of unresponsiveness in which patients lie with eyes closed, do not respond to attempts to arouse, and show no evidence of awareness of self or surroundings. Patients lack not only signs of awareness (similar to vegetative state) but also wakefulness (unlike vegetative state) regardless of how intensely they are stimulated. Patients typically either recover or progress to a vegetative state (that is, they show signs of wakefulness) within 4 weeks.

How is coma measured?

The depth of coma is measured by the Glasgow Coma Score (Table 4.8).

What is the minimally conscious state?

The minimally conscious state is a condition in which patients appear not only to be wakeful (like the vegetative state) but also to exhibit inconsistent (fluctuating) but reproducible signs of awareness (unlike the vegetative state). It may be a transient state and precede recovery of communicative function or it may last indefinitely.

What is locked-in syndrome?

Locked-in syndrome (or pseudocoma), although not a disorder of consciousness, may be confused with vegetative state. Patients are both awake and aware, yet entirely unable to produce any motor output or they have an extremely limited repertoire of behaviours (usually vertical eye movement or blinking). Numerous anatomical and aetiological types are possible, but a classic locked-in syndrome occurs with basilar territory infarction sparing respiratory drive centres but damaging long tracts and cranial nerve nuclei in the brainstem bilaterally. The cortex is

Table 4.7 Spectrum of disorders of consciousness

Condition	Definition	Main clinical characteristics	Consciousness		Purposeful motor behaviour
			Awareness	Sleep–wake cycles	
Coma	Unarousable state of unresponsiveness	Absence of eye opening (even with intense stimulation) No evidence of awareness of self or environment Condition protracted for more than 1 hour	No	No	No
Vegetative state	Wakefulness accompanied by the absence of any sign of awareness	Presence of eye opening and closing Absence of any reproducible purposeful behaviour including: (a) response to sensory stimulation; (b) awareness of self or environment; (c) language comprehension or expression	No	Yes	No
Minimally conscious state	Reproducible signs of awareness	Presence of eye opening and closing Presence of inconsistent but reproducible purposeful behaviour including (any of): (a) non-reflexive response to sensory stimulation; (b) awareness of the self or the environment; (c) language comprehension or expression Lack of functional communication or object use	Partial, fluctuating	Yes	Inconsistent
Locked-in syndrome	Impairment in the production of voluntary motor behaviour	Presence of eye-coded communication (limited to eye movements, depending on lesion) Preserved awareness Complete or partial inability to produce motor behaviour	Yes	Yes	Yes

Table 4.8 Glasgow Coma Score

Eye opening	
• Spontaneously	4
• To speech	3
• To pain	2
• No response	1
Best verbal response	
• Orientated	5
• Disorientated	4
• Inappropriate words	3
• Incomprehensible sounds	2
• No response	1
Best motor response	
• Obeys verbal commands	6
• Localises painful stimuli	5
• Withdrawal to pain	4
• Flexion to pain (decorticate posturing)	3
• Extension to pain (decerebrate posturing)	2
• No response	1

unimpaired but cannot deliver any of its actions. Patients can breathe and think normally but can perform few if any actions.

Why are coma and the vegetative state not the same as brain death?

In brain death there is loss of brainstem activity. Brainstem reflexes are absent and spontaneous breathing and circulation cannot occur and can only be maintained artificially. Only irreversible coma with absent brainstem reflexes indicates brain death.

What affects prognosis in patients with a vegetative state?

Three major factors affect the prognosis: time spent in the vegetative state, age and type of brain injury; traumatic brain injuries are associated with better outcomes at 1 year than non-traumatic injuries.

How is the vegetative state diagnosed?

No tool exists for quantifying the extent of consciousness. Differentiating between awareness and non-awareness ultimately relies on a principle that someone is conscious if they can indicate so. The diagnosis of the vegetative state is based on a detailed history and careful (but subjective) observation of the patient's spontaneous and elicited behaviour. Clinical assessments involve repeated examinations for evidence of: (a) awareness of self or environment; (b) sustained, reproducible, purposeful, or voluntary response to visual, olfactory, auditory, tactile or noxious stimuli; and (c) comprehension of language or expression. If evidence of these exists, the patient is considered to be (minimally) aware. Examinations should be conducted at different times of the day because patients who are minimally conscious as opposed to vegetative may have alternating periods of awareness and unawareness as well as circadian oscillations in levels of wakefulness.

Why do we provide life-sustaining treatments to patients in a vegetative state?

There are well-documented cases of recovery from a vegetative state, which is why it has been referred to as a persistent rather than permanent vegetative state. This said, it usually is permanent because of the nature of the underlying damage. Important considerations in the future care of a patient in a vegetative state are summarised in Box 4.32.

Does misdiagnosis of the vegetative state occur?

Current clinical methods of diagnosis are limited, evidenced by a high rate (about 40%) of misdiagnosis (that is, patients who are aware are considered to be unconscious). The main causes of misdiagnosis are associated with a patient's disability (such as blindness), confusion in terminology, and lack of experience of a relatively rare condition. Furthermore, standard behavioural assessments cannot distinguish an aware (minimally conscious) but completely immobile patient from a non-aware patient (vegetative state).

Is there a place for brain imaging as a diagnostic tool?

In such behaviourally non-responsive patients, functional neuroimaging methods (such as magnetic resonance imaging or electroencephalography) can detect residual cognition and awareness and can even establish two-way communication, without requiring any behavioural output from patients. The Multi-Society Task Force on PVS suggests, however, that such tests, although recognised as providing useful information when used in conjunction

Box 4.32 **Considerations in the future care of a patient in a persistent vegetative state**

- Establishing the diagnosis
- Deciding on its permanence
- The presence of any valid advance decision
- Deciding whether or not to withdraw life-prolonging treatments, which even in the presence of an advance decision often has to be decided in the Courts

with clinical evaluation, are believed to be unable, alone, to either confirm the diagnosis of vegetative state or predict the potential for recovery of awareness. Current guidelines should be modified to embrace functional neuroimaging.

CASE 4.36 BRAINSTEM DEATH

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Anne Daly, aged 58 years

Mrs Daly is a previously well 58-year-old woman admitted to hospital 2 days ago with collapse. She was intubated on arrival to hospital but subsequent brain imaging confirms that she has had a spontaneous subarachnoid haemorrhage. She has not received sedation since initial ventilation and shows no signs of recovery. Two consultants have confirmed brainstem death. She was previously well, and normotensive. Her daughter, Mrs Watts, is in the waiting room, aware that brainstem testing is being carried out although not completely aware of the implications of this.

Your task is to discuss the results with her daughter.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the daughter of Mrs Daly, a previously active 58-year-old woman. She was admitted to hospital 2 days ago following a fall whilst walking her dogs on the moor. She sustained a significant head injury. She was artificially ventilated on arrival to hospital and subsequent brain scans showed that she had sustained a large subarachnoid haemorrhage. She has subsequently shown no signs of recovery. She was previously well, and normotensive. You are aware that brainstem testing is being carried out, and although not completely aware of the implications of this sense that the news will be bad and that your mother is not going to recover. You are surprised that she is so desperately unwell, however, because her heart appears good on the monitor and she looks well but asleep. She carried a donor card, and you will tell the doctor this.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish that she is Mrs Daly's daughter.

2. Establish what the relative knows

Ask her what she knows about her mother's condition.

3. Explain the situation

Explain that there have been no signs of recovery of consciousness and that this has been the major concern.

4. Explain brainstem death

Explain sensitively and empathetically that, as a result of the injury, she has sustained irreversible brain damage and this has just been confirmed by the specialists. Explain that she will not wake up and that this means that she has died as a result of her injuries. Point out the ventilator is sustaining her breathing and that when turned off her heart would stop soon afterwards.

5. Acknowledge distress and allow ventilation of feelings

Wait for her response before giving any more details.

6. Explain what will happen now

Explain that the medical team has to make the decision to turn off the ventilator, that it will not cause her mother any distress, and that she need not feel any responsibility for this decision.

7. Discuss organ donation

Thank her for being able to mention this at this time. Assure her that as it is her mother's wish you will arrange for the transplant team to assess her mother for suitability, and until such time as any organ retrieval were to take place ventilation would be continued.

8. Identify support networks

It is human to want to discover a little more about the practical implications to her such as what other family members may be nearby and need to know, and even a little about the dogs.

9. Invite questions

Ask if she has any immediate questions.

10. Ensure that the relative has a point of contact

Ideally there would also be a nurse present to attend to her now but be prepared to meet her again later in the day or week if she has further questions.

Discussion

How might brainstem function be assessed?

Assessing brainstem function is vital to managing coma, raised intracranial pressure, brainstem strokes and confirming brain death.

Pupils assess midbrain integrity. Pupil size and reactivity assess third nerve function through the superior colliculus and connections to the Edinger–Westphal nucleus (midbrain) and efferent parasympathetic outflow.

The corneal reflex assesses the fifth and seventh nerves, connected in the pons.

Resting eye position might suggest asymmetric brainstem dysfunction, dysconjugate position a disorder of the third, fourth or sixth nerves or their nuclei (third and fourth in midbrain and sixth in pons). Spontaneous saccadic (fast) horizontal and vertical eye movements suggest that the brainstem mechanism for generating this is intact and there is no need to test for oculocephalic or oculovestibular responses. Horizontal saccades rely on an intact paramedian pontine reticular formation (pons), third nerve nucleus, sixth nerve nucleus and median longitudinal fasciculus connecting these. Vertical saccades rely on the dorsal midbrain.

Swallowing requires intact glossopharyngeal and vagus nerves and connections including the swallowing centre in the reticular formation of the medulla.

Respiratory pattern is sometimes useful in localisation. Apneustic breathing (prolonged inspiration followed by a period of apnoea) and cluster breathing (closely grouped respirations followed by a period of apnoea) imply pontine damage. Ataxic breathing (chaotic) and gasping breathing (gasps followed by variable apnoea) occur when the medullary respiratory centre is damaged and are precursors to respiratory arrest. Cheynes–Stokes breathing (often used to describe a range of brainstem damage patterns of breathing) can be due to cortical damage, but is mostly due to cardiovascular or respiratory disease. Slow, shallow breathing may occur when drugs depress medullary function. Central neurogenic hyperventilation (rapid, deep continuous breathing at a rate of around 25 cycles/min) is not localising but suggests deepening coma and worsening prognosis.

Long-tract signs can occur and may be crossed with cranial signs because of decussation.

What are oculocephalic and oculovestibular responses?

Passive head rotation stimulates vestibular and neck receptors which in comatose patients with intact brainstems leads to reflexive slow conjugate eye movements mediated by the vestibulo-ocular reflex (VOR) pathway in the brainstem in the direction opposite to head rotation. Ice water irrigation of the ear switches off this pathway, leading to the unopposed contribution of the contralateral vestibular system, and the eyes deviate towards the ice. Both the oculocephalic (doll's head manoeuvre) response and the oculovestibular (caloric) response test the VOR, but the latter is more sensitive.

Major brainstem pathology is unlikely with normal VORs. An absent horizontal VOR with an intact vertical VOR may indicate pontine damage. If both are absent there may be wider brainstem pathology or a metabolic disturbance, the latter more likely if pupils react. A very small number of drugs depress brainstem function. VOR testing may be difficult if there are dysconjugate eye movements (when brainstem dysfunction is likely) or if there are fast saccades (when brainstem dysfunction is unlikely).

Which brainstem syndromes arise from brain shift?

There are four important syndromes (Box 4.33).

Box 4.33 Brainstem syndromes arising from brain shift

Central herniation

A supratentorial mass displaces the diencephalons (cerebral peduncles, thalamic areas, thalamus and related structures between the cerebral hemispheres and upper brainstem) through the tentorium to compress the upper midbrain, then the pons, then the medulla. Signs such as unilateral hemiplegia, together with paratonia (gegenhalten) and extensor plantars (diencephalic stage), precede diminished alertness and Cheynes–Stokes breathing. The pupils are small, perhaps because of hypothalamic sympathetic dysfunction, but reactive. There is decorticate (flexor) posturing to pain. Progression from midbrain to upper pontine dysfunction causes temperature fluctuation, unreactive pupils in mid-position, loss of vertical eye movements (doll's head manoeuvre), diminishing vestibulo-ocular reflexes (VORs) and apneustic or cluster breathing or central hyperventilation. Decerebrate posturing to pain develops. Progression to lower pontine and upper medullary damage causes chaotic breathing and absent VORs. Tone is flaccid. Progression to medullary damage is terminal. Heart rate may fall and blood pressure rise (Cushing response), breathing is chaotic or gasping, and pupils become dilated and fixed.

Lateral (uncal) herniation

Lesions in the lateral middle fossa or temporal lobe push the medial edge of the uncus and hippocampal gyrus over the free lateral edge of the tentorium. The first sign is a unilateral dilating pupil as the third nerve is compressed, followed by a third-nerve palsy. Midbrain compression with diminished alertness and coma and the sequence as for central herniation can follow, without an initial diencephalic stage and decorticate responses.

False localisation

Expanding supratentorial lesions may distort structures and produce signs due to traction from afar, often affecting cranial nerves V to VIIII.

Tonsillar herniation

Subtentorial lesions may cause herniation of the cerebellar tonsils through the foramen magnum to compress the pons and midbrain directly. There may also be upward compression, giving rise to supratentorial effects, but the rostrocaudal sequence of damage typical of central herniation is lacking.

Table 4.9 Brain death criteria

Preconditions	Irreversible brain damage, e.g. head injury, brain haemorrhage, anoxia Apnoeic coma Absence of reversible factors such as drugs or metabolic or temperature disturbance
All brainstem reflexes absent	Pupils fixed and unresponsive to bright light (not necessarily dilated) Absent corneal reflexes Absent vestibulo-ocular reflexes No motor responses within the cranial nerve distribution to stimulation of any somatic area No reflex response to touching the pharynx (gag reflex) or a suction catheter in the trachea (cough reflex)
Apnoea	No respiratory movements without the ventilator

How is brain death determined?

There is irreversible loss of capacity for consciousness and capacity to breathe. Both of these are lost without the stem. Because it is possible to maintain circulation and ventilation with ventilators in patients with irreversible brain damage without brainstem function, criteria for brain death were developed (Table 4.9). Testing should be by two experienced clinicians, at least one a consultant.

Is there a legal definition of death?

There is no legal definition of death. Death is usually defined by irreversible loss of capacity for consciousness together with irreversible loss of capacity to breathe due to cessation of brainstem function. Brainstem death therefore equates to death of an individual.

CASE 4.37 DISCUSSING LIVE ORGAN DONATION

Candidate information

Role

You are a doctor in the renal clinic.

Please read this summary.

Scenario

Re: Mr Stephen Wells, aged 45 years

Mr Wells, a solicitor, has chronic kidney disease due to diabetes mellitus on a background of poor renal reserve caused by damage from sepsis as a child. He currently receives haemodialysis. He is on the transplant list. His sister is with him today because they have both discussed the idea of live organ transplantation, having read of its success. Her concerns are the risks to her and her brother.

Your task is to discuss live organ transplantation.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the sister of Stephen Wells, a 45-year-old solicitor who has chronic kidney disease from diabetes mellitus and kidney damage as a child. He currently receives haemodialysis. He is on the transplant list. You are with him today because you have both discussed the idea of live organ transplantation, having read of its success. Your concerns are the risks to yourself and your brother, but you would prefer your brother to have your kidney than one from an unknown source, and feel his body would not reject an organ from a relative.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself. Both potential recipient and donor should be present (in PACES only one subject but the principles are the same).

2. Establish background knowledge

Find out what they know about organ donation.

3. Explore ideas, concerns and expectations

Explore their understanding of the advantages of live organ donation. Explain that there are very clear advantages but that the complications of transplantation, including rejection, remain a risk.

4. Explain the principles of live organ donation

Explain briefly there would be a dual hospital stay for the operation but that the surgical procedure is not your area of expertise and you would arrange a meeting with the transplant surgeon were they to decide to go down this route.

5. Respond to ideas, concerns and expectations

Explain that matching is a potential problem but that it needs not be perfect nor, indeed, need it be a relative. Her being a sibling does not remove the possibility of rejection and he will still need to take immunosuppression with its attendant risks.

6. Explain potential benefits to recipient and donor

Explain that outcome is better with donation from a live than a deceased person. While on the waiting list there is no guarantee of when a suitable organ will be available and his health might deteriorate in the meantime; live organ donation would remove this problem. There may be significant psychological satisfaction in donating to a relative.

7. Explain potential risks to recipient and donor

Risks to the donor include operative and perioperative risks (major surgery requiring around a week in hospital and some weeks off work), and having a single kidney (although compatible with a normal life). Risks to the recipient are immediate surgical complications and rejection.

8. Other matters

There may be insurance issues for the donor.

9. Invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

Be honest in your explanations and prepared to admit uncertainty (with assurance you will seek the answer) if there are questions you cannot answer.

10. Explain what would happen next

Explain that, if they decide to take things further, formal assessment by the transplant team would be needed.

Discussion

How is organ transplantation governed in the UK?

Following the retained organs controversy (Case 4.38), the Human Tissue Act in 2004 introduced new legislation and regulation for all human material, whether from living or deceased people. It applies to England, Wales and Northern Ireland and the Scottish Assembly passed similar legislation in 2006. The Human Tissue Authority (HTA) is the body that ensures that human tissue is used safely and ethically, and with proper consent. The HTA regulates the removal, storage, use and disposal of human bodies, organs and tissues for purposes such as research, transplantation, and education and training, and gives approval for organ and bone marrow donations from living people. It was created by the Human Tissue Act 2004, which replaced the Human Tissue Act 1961, the Anatomy Act 1984 and the Human Organ Transplants Act 1989. The Unrelated Transplant Regulatory Authority (ULTRA) and the post of HM Inspector of Anatomy were abolished and their functions transferred to the HTA.

Is there a shortage of organ donors?

There is a worldwide shortage of cadaveric donor organs, and a living related donor is more likely to provide the best histocompatibility but more likely to feel pressure to donate. Shortage of organs is doubtless in part the result of the understandable reluctance of staff to approach relatives for consent after a patient dies.

How might the supply of organ donors be increased?

The situation could be improved by educating the public to leave evidence of their wishes, reducing the need to broach the subject with grieving relatives. The default position of a population opting in to donate is mooted by governments.

Does the Human Tissue Act improve the number of organ donors?

Currently, even if the deceased carries a donor card, a relative's objections can prevent transplantation. The Act ensures that the patient's recorded wishes, or the decision of a representative nominated by the patient, must be followed. Failing this, consent from a person in a 'qualifying relationship' is necessary (there is a hierarchical list). The Act unambiguously outlaws all commerce in human bodies and body parts.

Can dying patients who are potential donors be 'kept alive' in intensive care while consent is being sought for organ donation?

Donor ventilatory and circulatory support is essential before heart transplantation and desirable for other organs. Transplantation procedures can only occur when brainstem death has been determined, and this should be by a team separate to that caring for the patient. 'Elective ventilation', the concept of sustaining the life of a dying patient for the sole purpose of transplantation, appears to be illegal, but the Act authorises methods to preserve organs of deceased individuals while consent is being sought.

Are there advantages of live organ donation?

Carefully selected living related donors are more immunologically compatible and the chances of graft rejection are reduced.

What ethical criteria should be met by live organ donors?

These are listed in Box 4.34.

Is there a place for unrelated live transplants?

A donation may be obtained from a non-genetically-related person provided no payment is involved. Historically, live unrelated donors of kidneys were seldom considered because there was no greater chance of graft survival, but modern immunosuppression means that less well-matched grafts can now survive.

Box 4.34 **Criteria for live organ donors**

- The risk to the donor must be low
- The donor must give full informed consent
- The consent must be given freely and without coercion or pressure
- The donor must understand that he or she may withdraw consent at any time before the procedure
- The offer of the organ must be without any inducements, including financial
- There must be a good chance of a successful outcome for the recipient

Box 4.35 **Common reasons for requesting an autopsy**

- The cause of death was not clear
- Whilst the cause of death may have seemed clear, some features of the disease remain unusual
- The disease was rare and an autopsy could shed new light on it
- The information from the autopsy might help the management of other patients (in some cases family members) who suffer from the same condition

CASE 4.38 REQUESTING AN AUTOPSY (POST MORTEM)

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Jane Ayre, aged 76 years

Mrs Ayre was a 76-year-old woman who died yesterday on your ward. She had been admitted with weight loss, vomiting and hypotension. She was awaiting further investigation after an abdominal computed tomography scan showed bilateral adrenal masses. The concern had been whether she might have adrenal metastases and secondary hypoadrenalism. Her daughter is here, and your consultant has asked you to seek permission for an autopsy to clarify cause of death, but is happy for a death certificate to be issued if she does not consent.

Your task is to request permission for an autopsy.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Your mother, Mrs Ayre, died yesterday on the hospital ward, aged 79. The cause of death was unclear but very possibly cancer. She had been admitted from home following 1 week of vomiting and dizziness. She had been losing weight for a few months prior to this. She and you had been told that cancer was a possibility although you had not expected her to die so suddenly. The doctor is about to ask your permission for an autopsy. You are not happy for an autopsy, feeling that if cancer was likely there is no reason to further explore. You are also worried an autopsy could delay funeral arrangements and cause disfigurement. After consideration, you will agree to an autopsy.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Acknowledge that it is a difficult time

Tell her how sorry you are that her mother has died and that staff members were saddened by the news. Pause to allow her to express her emotions. Asking for permission to carry out an autopsy at a time when relatives may be distressed is not always easy and not a task that should be delegated to the most junior member of the team. Before approaching relatives, it is important to establish if the patient had made any prior wishes.

3. Retrace the relevant background

Explain the medical team's thoughts about what might have been wrong with the patient and why.

4. Explain the reasons for requesting an autopsy

Common reasons for requesting an autopsy are listed in Box 4.35.

Additional benefits include education and training, research and audit.

5. Explain the autopsy consent form

Explain that she will need to sign a consent form. This includes an option for relatives to request a limited autopsy, with separate sections for permission for organ retention, permission for education and training and permission for the use of retained tissue in research.

6. Explore concerns

She may have concerns about further examination when all she wants, and she feels her mother wants, is to be left in peace.

7. Be prepared to discuss arrangements about the body

Explain that an autopsy will not (usually) delay funeral arrangements. Relatives sometimes ask if the body can be viewed after autopsy and might need to be reassured that in hospital autopsies standard incisions are used that are not visible when the body is gowned and that the body can be viewed after autopsy.

8. Invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

9. Explain what would happen next

Explain that nothing needs to be done by the daughter, that the hospital would arrange everything and that the funeral director would liaise with the hospital directly.

10. Seek consent or accept refusal

And thank her for discussing this.

Discussion

What changes have occurred in recent years in the law regarding retention of human tissue and organs?

The public inquiries at Bristol Royal Infirmary and Alder Hey Children's Hospital found organ retention without the knowledge or consent of relatives to be common practice. The Chief Medical Officer subsequently arranged a consensus that revealed 105 000 retained organs, body parts, stillbirths and fetuses within English hospital trusts and the Retained Organs Commission was set up to oversee the return, donation for research or disposal of retained material according to the wishes of relatives who enquired, and to advise on future legislation.

The Human Tissue Act makes it a criminal offence to remove, retain or use tissue or organs without consent and covers all material containing human cells removed from the living or dead (gametes or embryos are covered by separate legislation). Thus no research or teaching is now possible without consent. Use for clinical or public health audit, education or research using anonymised material does not require consent if the material comes from the living, but will always be needed if from deceased persons. The Act is not be retrospective, but the Human Tissue Authority, the regulatory body for the Act, issues codes of practice for dealing with material already retained.

What is the role of the Human Tissue Authority?

It is to regulate the removal, storage, use and disposal of human bodies, organs and tissue from the living and deceased.

What are the implications for hospital autopsies?

Most hospital trusts have guidelines for autopsy requests. Most autopsies in hospital are hospital requested and performed by a hospital pathologist, and for these relatives must grant permission.

Consent forms usually cover the option for relatives to request a limited autopsy, and separate sections for permission for organ retention (usually brain or lungs), permission for education and training (often a clause stating that information may be used for such purposes unless relatives disagree) and permission for the use of retained tissue in research.

Disposal of organs retained can either be by the pathology department or returned to the funeral director at the family's request.

There is concern that hospital autopsies will decline in number, and training will suffer, although the legislation acknowledges that people expect clear information and partnership with the medical profession. Hospital trusts must therefore produce clear procedures and consent forms and adequate training in gaining consent from relatives.

In which circumstances might the coroner (in Scotland Procurator Fiscal) wish to perform an autopsy?

While the statutory duty to report a death to the coroner resides with the registrar of births and deaths, doctors should be aware of the circumstances in which a registrar is required to report a death and should report a death themselves in those circumstances (Box 4.36).

Box 4.36 **Deaths that should be reported to the coroner**

- Deaths that are sudden or unexplained
- Deaths where the deceased had not been attended by a medical practitioner for their last illness and within 14 days before death
- Deaths not due, or entirely due, to natural causes, e.g. accidents, deaths occurring after an operation, occupational disease, lack of care, self-neglect, suicide and self-harm, violence
- Deaths involving septicaemia if originating from injury or medical intervention
- Dead on arrival to hospital
- Deaths in police custody or prison or following admission from these
- Deaths where the cause is natural but unknown and the doctor cannot issue a death certificate

Does a coroner's autopsy need consent?

No. Relatives do not have the right to either grant or refuse permission for an autopsy requested by the coroner, nor any organ retention, although the Act will make it necessary for consent to be obtained for retention or use of material after investigations are concluded.

Clinical governance

CASE 4.39 CRITICAL INCIDENT

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Mrs Jane Parker, aged 84 years

Mrs Parker was admitted 3 days ago with life-threatening haematemesis. She had a history of a stroke from which she had made a partial recovery. You resuscitated her with blood. The gastroenterologist requested central access for monitoring purposes while preparations were made for endoscopy. This was a difficult procedure because her systolic blood pressure was 80 mmHg. Eventually you obtained flashback of dark-red blood in the left internal jugular region and gained access. At endoscopy a bleeding gastric ulcer was injected and she was admitted to the high-dependency unit (HDU).

The gastroenterologist met you yesterday to let you know of a critical incident. The day after admission to the HDU Mrs Parker suffered a further stroke with dense left-sided weakness and a computed tomography scan showed a very large right parietal infarction, probably from watershed ischaemia. It was also noticed in the HDU that your central line was positioned in the left carotid artery. It had not been used, although for reasons not yet established had not been removed despite a chest X-ray showing malposition. Unhappily, the HDU doctor told Mrs Parker's daughter that arterial catheterisation should never occur because it can cause a stroke. You honestly cannot recall reviewing the chest X-ray.

The gastroenterologist is convinced that the stroke was caused by hypotension on a background of a cerebrovascular disease, not least because the stroke occurred on the wrong side to implicate the catheter. He is also very irritated by the careless remarks of the HDU doctor. However, he feels that the incident should be reported because although unlikely to be causative, and a well-recognised complication of the procedure, a system failure led to the potentially dangerous situation of non-removal of the malpositioned line. He has spoken to the daughter and given these views. However, the patient's daughter, with whom you spoke on admission, would also like to talk to you.

Your task is to talk to the daughter and respond to her concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Your mother, Mrs Jane Parker, is an 84-year-old woman who was admitted to hospital 3 days ago with a bleeding stomach ulcer. She had a stroke 2 years ago, leaving her relatively immobile and she lives with you. She has continued to have 'mini-strokes' with effects on mobility and memory and you have been concerned about her quality of life. At endoscopy the bleeding ulcer, which you accepted as life threatening, was treated and she was admitted to the highdependency unit (HDU) because of very low blood pressure. You were very happy with the admitting doctor's (the candidate's) communication to you of events. Subsequently, your mother has had a stroke and is now very unwell. You were not surprised by this, although you were upset when another doctor, in the HDU, told you that the admitting doctor had placed a catheter incorrectly into the artery of her neck and that this probably caused the stroke. The consultant has subsequently made you feel easier, explaining that the line was placed incorrectly, but that it does not seem to have been the cause of the stroke but that the matter will be looked into thoroughly. You believe the consultant, have no wish to make a complaint because you have been very happy with the care given to your mother over the years and accept that she has been unwell for some time. However, you would like to speak to the admitting doctor, both to hear his view of events and to be further reassured that the HDU doctor was 'out of line'.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction and setting

Show that you are willing to listen, explain and help in whatever way you can. Angry or upset patients and relatives should never feel threatened.

2. Listen to concerns

Allow her to say what she wants to, without interruption. Find out the exact nature of her concerns. More often than not, venting of emotions is what people want, in this case concern and likely confusion created by the careless words of a colleague.

3. Acknowledge concerns

First and foremost, make her see that you understand her concerns. Make it very clear that you and the consultant are concerned about the incident. Tell her that she has a right to know exactly what happened.

4. Apologise, if appropriate

Where it is clear that a mistake has been made, say how sorry you are that the incident occurred. In this case, however, you should not admit to the allegation of the HDU doctor but you do want to concede that a recognised complication of the procedure occurred. You may also need to say how sorry you are that she has been upset and confused by apparently conflicting comments.

5. Do not criticise colleagues but give your view

Colleagues have the same rights to be consulted and given the opportunity to seek advice, and ill-considered remarks could lead patients or relatives to misleading conclusions and prejudice a colleague's interests. Colleagues should never be criticised openly, but this does not necessarily mean dismissing or excusing a patient's or relative's expressed concern or complaint. While you should not criticise the HDU doctor (no matter how you may feel about his careless remarks) it is appropriate to say you agree with the comments made by the consultant, reinforcing what you see as correct information. Overall, you need to let her see how sorry you are that her mother's condition has deteriorated, without focusing so much on the HDU doctor's view.

6. Explain how the incident occurred

Explain, as clearly as possible, how the incident occurred. Explain that your action was in good faith in the best interests of her mother, who was very unwell, and that you were deeply concerned to learn that you had placed the catheter in the artery as soon as it became known to you.

7. Work with facts – do not speculate!

Since you should work with facts, do not speculate as to why the catheter was left incorrectly *in situ* until the facts have been established.

8. Give an assurance of further action

Explain that normally mechanisms should be in place to recognise such a complication (chest X-ray + /− blood gases). Tell her that the incident will be reported as a 'critical incident' to the risk management team, who will investigate it further and decide what action might be taken to avert such an incident in future (the use of Doppler-guided central line placement is now considered best practice).

9. Invite questions and provide further information if needed

Ask if there are any other specific concerns she has not mentioned. Hopefully she accepts your candid response to the incident but if she wishes to make a formal written complaint she should be informed of to whom to write. In any event, you should offer to be of further assistance should she have further questions or concerns.

10. Document everything fully and carefully

The vast majority of critical incidents are errors not of one person but of a system within which fallible people operate. Discuss the incident with your consultant, document everything clearly and depending upon the significance of the incident discuss it confidentially with your medical defence organisation.

Discussion

What do you understand by the term clinical governance (CG)?

The full definition, originally from the government paper 'A First Class Service 2000', is 'a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish'. In short, it means striving for the best quality, minimising harm and maximising benefit within budget and resources.

CG was given impetus by health-care disasters like Shipman and the Bristol Enquiry. Key areas of CG are outlined in Box 4.37. Ideally, CG should be proactive, but it often needs to react to complaints, claims and incidents.

What is a critical incident?

A critical incident is an event that gives rise to, or has the potential to produce, unexpected or unwanted effects involving the safety of patients. It is a serious event that harmed or could have harmed and as such would be likely to give rise to public concern or criticism of the service involved. Annually in the NHS there are known to be around 850 000 adverse events and 28 850 000 complaints. This may be the tip of the iceberg. Trusts have clinical risk management teams to aid investigation of clinical incidents and many have their own legal department and solicitors.

Should you report all incidents?

All incidents should be reported, but, because of the enormous number of them, grading systems or risk matrices

Box 4.37 **Key areas of clinical governance**

- Clinical risk management, e.g. incident reporting
- Education and training, e.g. standardised outcomes and assessments
- Patient and public involvement, e.g. expert patients, copying letters to patients
- Staffing, e.g. appropriate selection
- Effective communication and use of information, e.g. use of computerised imaging and electronic patient records
- Audit, e.g. local, national
- Research, evidence-based practice and clinical effectiveness, e.g. use of National Institute for Health and Clinical Excellence guidelines

have been introduced that incorporate both their likelihood and their consequence, to give priority to the more serious.

What do you understand by the term system error?

Seldom is one individual wholly responsible for a critical incident. The role of risk management teams is to investigate the system within which individuals operate to identify gaps that expose it to errors. The above case illustrates such gaps (e.g. the use of Doppler imaging for inserting central venous catheters, chest X-ray confirmation post-procedure and the question of who is responsible for checking it if a patient moves to a different team's care). Incidents happen because of failures in the organisation's management, local conditions (e.g. understaffing, tiredness, under-resourced), individual unsafe acts (e.g. missing out a step in a procedure because short of time or multitasking) and what has been called 'the final defence barrier breach' (e.g. in an adequately staffed procedural room, a doctor may have omitted to check the date and label on the local anaesthetic but a nurse might have noted it). For these reasons alone, it is never acceptable to rush to blame.

What is the National Patient Safety Agency (NPSA)?

Everyone makes mistakes. The questions are why are they made repeatedly, how can we learn from them and can we eliminate some of them. The NSPA takes a seven-themed approach to this (Box 4.38).

Box 4.38 National Patient Safety Agency (NPSA) approach

Promoting a safety culture

This includes enhancing awareness and building safety into daily work with such activities as induction, handovers and audit.

Leading and supporting staff

This includes clinical leadership and supporting staff ideas.

Integration of risk management activity

This includes working across teams, departments, trusts and the NHS, e.g. the tracking of blood for transfusion from source to patient. It embraces all information such as incidents, complaints, litigation and audit, and balances costs with levels of risk. It is not feasible, for example, for all surgical instruments to be single use. Risk management at the directorate level includes risk and medical management, critical incidents and audit, and at the governance committee level are a health and safety committee, evidence-based practice, infection control and so forth.

Promotion of reporting

This includes reporting of incidents, near misses and methods for investigation and review (information, mapping of event, barriers to safety). Barriers to safety include discontinuity of care, communication failure and the different layouts of each ward, and barriers to reporting include fear of blame, no clear benefit, 'not my job', no feedback or 'a waste of time'. A non-punitive atmosphere is essential to promote reporting.

Communication with patients and public

Key principles are honesty, apology, explanation and thorough investigation.

Learning and sharing lessons

Information needs to be disseminated by, for example, email, written memos, policy documents and discussion.

Implementation of solutions

A National Confidential Enquiry into Patient Outcomes and Deaths (NCEPOD), for example, under the NPSA, recommends more consultant involvement in clinical care to recognise and manage critical illness.

How is a hospital managed?

A Trust Board has overall responsibility for scrutinising trust policy, implementing national / government policies and advising the Trust Executive. The Trust Board comprises a chief executive together with executive and non-executive directors. Board executives are usually ex-bankers or lawyers or business people, and sometimes nurses.

The Trust Executive is the hospital's functioning body. It comprises clinical directorates and corporate directorates.

Clinical directorates typically include medicine (usually enormous), general surgery, specialist surgery, trauma and orthopaedics, child and women's health, critical care / emergency medical services, diagnostic services and professional services. Each clinical directorate provides services, e.g. the disciplines of general medicine and specialist medicine within the Medicine Directorate, and physiotherapy, occupational therapy, speech and language therapy and dietetics within the Professional Services Directorate. Each clinical directorate comprises a Clinical Director (CD), directorate manager, a lead nurse and a directorate accountant. These are all responsible to the Medical Director, who in turn is answerable to the Chief Executive. These people meet regularly. The CD is usually a doctor, who relies very much on the directorate manager as he or she usually struggles to combine CD work with clinical work. Roles include ensuring clinical and operational performance, changing strategies within the trust in line with national policies and working with primary care trusts. Much work is 'fire fighting' – handling complaints, approving study leave and so forth.

Each corporate directorate comprises a director and provides certain services. Corporate directorates might typically include the Chief Executive, the Medical Director, finance and information management and technology (IM&T), human resources (staffing, occupational health), operations (e.g. clinical directorate management, operational performance, business planning, emergency preparedness), facilities (e.g. estates, catering, laundry, parking, security, fire, bookshop), nursing and service improvement (e.g. complaints handling) and planning.

The flow of NHS money is from the Department of Health, which feeds it to primary care organisations, which feed via the Planning Directorate to NHS trusts (linked to strategic health authorities), who set their own budgets.

What do you know about the Access to Health Records Act?

This gives patients the general right to see their medical records, obtain copies thereof and have the records explained to them. It applies only to records after 1 November 1991. A doctor may deny access (it is not that the whole record should be withheld but only specific information within it) on the grounds that it is 'likely to cause serious harm to the physical or mental health of the patient or any other person, or could lead to the identification of another individual (other than the health professional) who has been involved in the care of the subject'. An application must be in writing and made by a patient, person authorised by the patient, person appointed by the Court or an executor. When application for access is made by an individual on behalf of a patient who is incompetent or deceased, no information can be given that the patient had considered confidential and the holder is not required to explain why any part of the record has been withheld. Viewing of the records should be provided within 21 days (40 days for records at least 40 days old). A reasonable fee may be charged.

CASE 4.40 MANAGING A COMPLAINT AND THE QUESTION OF NEGLIGENCE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mr Jeremy Finch, aged 64 years

Mr Finch is a 64-year-old man on your ward who last week had an endobronchial biopsy for a suspicious lung lesion. Yesterday evening he was told by a member of staff (you are not yet sure who), in the presence of his daughter, that the lesion might well be benign, and yet this morning you received the formal report suggesting it is an adenocarcinoma. You discussed this sensitively and Mr Finch seemed to accept the diagnosis but his daughter now wants to talk to you.

Your task is to address his daughter's concerns.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the daughter of Mr Jeremy Finch, a 64-year-old man who has been told by his doctor this morning that the result of his lung biopsy is that he has lung cancer. You are understandably upset although you had been concerned for some time that he had been coughing up blood and it took you some months to persuade your father to come to hospital. You are, however, very upset that yesterday evening a junior doctor on night shift came to take blood from your father with you present and commented that very often these turn out to be benign. You are concerned because this is not the first 'disaster'. When your father was first admitted he was told he had pneumonia and given a dose of penicillin when it was documented very clearly in his general practitioner's referral that he was allergic to penicillin. You feel that the hospital makes one mistake after another and want to complain and may consider suing the hospital for negligence.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction and setting

Introduce yourself and confirm her identity. Show that you are willing to listen, explain and help in whatever way you can. Angry or upset patients and relatives should never feel threatened.

2. Listen to concerns/complaint

Allow her to say what she wants to, without interruption. Do not take any criticism personally. Find out the exact nature of her complaint. More often than not, venting of feelings to a sincere and responsible listener is enough for patients or relatives. Progression to a complaint is less likely if you can facilitate this.

3. Acknowledge concerns

Let her see that you understand her grievances, and are dedicated to responding to these appropriately.

4. Apologise, if appropriate

Where it is clear that a mistake has been made, say how sorry you are that this incident occurred. Unless it is very clear that a complaint is unreasonable, it is always best to offer a sincere apology, and, if unreasonable, to say you are sorry the person feels that way.

5. Do not criticise colleagues but give your view

Focus on any problem in the system, not on any individual.

6. Explain how the incident occurred

Explain, as clearly as possible (if you know), how the incident occurred.

7. Work with facts – do not speculate!

It is inappropriate to speculate (or worse, ascribe blame) when you do not have all the facts; these should be established, if need be, by proper inquiry. Emphasise the clinical imperatives – to now seek advice from the respiratory and cancer specialist about the best way to treat her father's condition.

8. Give an assurance of further action about the complaint

Tell her that you will share the information with your consultant and report the incident as a 'critical incident' to the risk management team, who will investigate things further and decide what action might be taken to avert such an incident in future.

9. Invite questions and provide further information if needed

Hopefully she accepts your candid response to the incident but if she wishes to make a formal written complaint she should be told to whom to write. In any event, you should offer to be of further assistance should she have any further questions or concerns.

10. Document everything fully and carefully

The vast majority of critical incidents are errors not of one person but of a system within which fallible people operate. Discuss the incident with your consultant, document everything clearly and depending upon the significance of the incident discuss it confidentially with your medical defence organisation.

Discussion

Why do people make a complaint?

People complain to vent anger, seek changes, receive an apology, feel better, blame someone else and stop the same thing happening again. Sometimes they complain seeking compensation. People complain about clinical care, staff attitudes, outpatient delays, poor communication, discharge and aspects of non-clinical care.

How might complaints be avoided or minimised?

Knowing why people complain can help minimise complaints. Every effort should be made to avoid dispute or altercation. The General Medical Council recommends that patients and relatives have a right to expect prompt, open, constructive and honest responses to their concerns. This will include an explanation of what has happened and, where appropriate, an apology. Communication is the key to 'damage limitation', while withholding facts or retreating behind a wall of silence can inflame concerns. Clear documentation is the key to defending actions now that may be questioned at any time in the future. Happily, gratitude is overwhelmingly more common than complaints.

Must you cooperate with a complaint, even if you disagree with the person making the complaint?

You must cooperate fully with a complaint or formal inquiry, although any complaint made that demands more than an initial verbal response should be handled by the complaints procedure. You must provide information as to whom to write – the complaints manager/complaints department, through whom all complaints are managed.

What are the purposes of NHS complaints procedures?

These are to resolve a patient's complaints (e.g. by explanation or apology) and to improve NHS services. Where compensation is sought, this is no longer a complaint to be managed by the complaints department, but a claim, and the patient must seek legal representation.

What are the general levels of complaints procedures?

There are two levels to which a complaint might go (Box 4.39). Most are locally resolved, with a response within 20 days.

Can an NHS complaints procedure be used to discipline a doctor or award compensation?

No.

Box 4.39 **Levels of complaint**

Local procedures

- Attempt to resolve complaints by local staff and managers

NHS ombudsman

- Can investigate, if certain criteria are fulfilled, usually in matters of maladministration
- Ombudsman decides whether to investigate, conducts investigation and reports to the NHS body involved, disseminating findings widely and implementing action needed

What sorts of medical error occur?

Common errors in order of frequency are:

- Failure or delay in diagnosis
- Medication error
- Unsatisfactory management
- Failure of supervision
- Complication of procedure
- Injury.

Common missed acute diagnoses (which may lead to a negligence claim) are:

- Myocardial infarction in younger women
- Infective endocarditis (often because investigated through a care pathway, e.g. anaemia investigation)
- Subarachnoid haemorrhage (with reliance on computed tomography imaging, which misses 10%)
- Meningitis with delayed antibiotics
- Diabetic ketoacidosis
- Hyponatraemia due to Addison's disease
- Occult neoplasm
- Alcohol-related Wernicke's encephalopathy or subdural haematoma
- Asthma being diagnosed without a peak expiratory flow rate
- Pneumonia without early antibiotics
- Pulmonary embolism and deep vein thrombosis
- Medication error.

What are the conditions for negligence?

People often use the term professional negligence loosely to mean bad clinical practice. The legal definition is much more precise. Legal action for negligence is the patient's claim for compensation for losses caused by the professional. For a successful claim, all of the conditions in Box 4.40 must be proved.

These four conditions may be summarised as 'duty, deviance, damage and due to'.

Box 4.40 **Conditions for negligence**

1. The professional had a duty of care to the patient

The law imposes an onus on a doctor only if a professional relationship exists between the doctor and the patient. The doctor has particular knowledge and skills and the patient consults them, as when a patient consults their general practitioner or is cared for by a doctor in hospital. A duty of care does not exist for strangers ('Good Samaritan' acts), although a doctor may become liable if he or she proceeds to treat improperly or causes harm. It is usually easy to establish whether a duty of care exists.

2. The professional was in breach of the appropriate standard of care

A patient must show that the doctor did not fulfil his or her duty. Doctors have a broad range of duties including making appropriate diagnoses, giving appropriate treatments and ensuring that patients are fully informed so that consent is valid. However, it is well known that equally knowledgeable, skilled and experienced doctors may tackle a case differently. Therefore the Courts have used the 'Bolam test' to decide whether a duty of care has been breached – that duty is not breached if a 'responsible body of medical opinion would have acted in the same way in the same situation'. It is also accepted that experts differ in opinion (e.g. treating cough, sputum and fever with antibiotics or considering it viral) and either may be acceptable. The test, however, must be that other experts would have done the same, and not 'that could have happened to me, I could easily have found myself in that situation'; the latter analogous to driving at 40 mph in a 30 mph zone.

3. Harm resulted

Negligence cannot be considered if no damage was incurred, even if there was a breach of duty.

4. The breach of duty caused the patient's harm

The patient must show that the doctor's mistake or failure or action caused the injury or other losses. This is the most difficult condition to prove, as breach of duty and harm may both have occurred, but that the former caused the latter does not necessarily follow.

Is there a time limit for suing for an act of alleged negligence?

A patient must sue within 3 years of the act of alleged negligence. For a complaint the time limit is 6 months, often extended to a year.

Are individual doctors or trusts sued?

Before 1990 a patient or relative who wished to make a civil claim as a result of NHS care sued an individual, named doctor or health-care professional and the defence of the claim was handled by the relevant defence organisation. Since then 'Crown indemnity' has been introduced, and it is the trust that is sued and the case is investigated and defended by the hospital's legal team, solicitors and the NHS Litigation Authority. The NHS Litigation Authority has developed as a powerful centralised legal body for the NHS. It decides on the basis of the four 'D's if it thinks the case if defendable, which in most cases it will be. Where clearly indefensible (e.g. wrong finger amputated), it will attempt to settle out of court rather than proceed to civil court proceedings. Doctors are therefore witnesses in proceedings and not personally liable for payment of legal costs or damages, but their involvement in a claim may be considered as a separate issue by the trust's consultants or directorates.

Are damages awarded in cases of negligence punitive?

Any damages awarded aim to meet losses incurred, but not to exceed them. In other words, punitive damages are not awarded.

What are vicarious liabilities?

NHS employers may be covered for cases of negligence by the Crown Indemnity Scheme. Patients may sue health professionals personally but, provided certain conditions are fulfilled, they may choose to seek compensation from the employer. The advantages of vicarious liability to patients is that more substantial claims for damages may be affordable to employers and, if action is brought many years after an event, the health professional may be harder to trace.

What is an inquest?

This is a fact-finding enquiry about a reported death, conducted by the coroner, who requests written and sometimes verbal evidence from a variety of sources. It is not a trial. There are no parties, and there is no indictment, prosecution or defence. Possible verdicts in order of decreasing likelihood include natural causes, accidental death, industrial disease and unlawful killing. The verdict for a patient who has died from complications following an operation may be accidental death because the operation was planned but the outcome was not. An open verdict is returned if the coroner believes there is insufficient evidence to reach a decision. The coroner's court is a public court and the press may attend, as do a hospital's legal team.

CASE 4.41 FITNESS TO PRACTISE – POOR PERFORMANCE IN A COLLEAGUE

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Dr Stephen Cotton, aged 25 years

Dr Cotton has been your F1 doctor (house officer) for 1 month, having worked on a different ward for 3 months beforehand. He has a further 2 months with you. You think his medical knowledge is sound and do not doubt his genuine intention to be a good doctor because he clearly works very hard and stays late after work to complete tasks he has been unable to complete during the day. However, his work is ineffective. You believe his main problem is inability to prioritise tasks. He tends to respond to every request made of him by nursing and other staff immediately, although dropping what he is doing in the process. If he is on your ward round, for example, and a nurse tells him a drug chart needs to be written in the next bay, he will leave to rewrite the drug chart. He seems to see every task as equally weighted. Furthermore, when he is on your ward rounds he does not appear to listen to instructions or advice because he seems too nervous about all of the jobs he has to do. You can cope with a weaker member of the team, but are aware that colleagues are increasingly frustrated by his performance. Some laugh about it behind his back. You feel he could benefit from confidential support and advice.

Your tasks are to explore his poor performance and offer constructive advice.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Dr Stephen Cotton has been an F1 doctor (house officer) for 4 months. He found his first 3-month post enormously difficult because there was simply too much work, and he was constantly being bleeped with more of it. Other staff seemed not to be pulling their weight. He felt out of his depth, and he found the F2 doctor (senior house officer) was never there to help or advise him. He felt he did not know what he was doing much of the time, and so simply did what everyone – usually nursing staff – told him to do. This frustrated him, as he was a very good student and had great hopes of being a good doctor. For the past month he has been in a different post where the senior doctor is very helpful, but he is still not sure that he is performing well. He has heard colleagues in the hospital mess laughing about him because of his inefficiency but he does not know how he could work any harder. His senior colleague is about to talk to him about his performance.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction and setting

Ensure you have time to talk with him, in a non-pressured environment, and make it clear the discussion is confidential.

2. Open diplomatically

Telling someone they are no good does not open dialogue. Tell him that you wanted to discuss his experiences of the post so far. Explain that it is often difficult to judge how a relatively new doctor is feeling about the job, although it has become apparent to you that he works exceptionally hard and feels a sense of duty to respond immediately to every request.

3. Make it clear you are there to offer constructive help

Explain that this is an impossible task for any doctor and if there are strategies to make the burdens of the job seem easier, and the remaining 2 months as educationally valuable as possible, you would like to try to identify these.

4. Listen to the experiences of the poorly performing doctor

Listen supportively, as the last thing he needs is for everybody to takes sides against him. Allow him to tell you how he sees the job, which might be very different from how you or your colleagues see it.

5. Share the good points

Show understanding of how a house officer's job is difficult – doctors must adjust from the learning environment of medical school to the intensely practical and often mundane tasks of clinical work; when emergencies happen you can feel out of your depth; support can sometimes seem lacking; there always seems to be too much work and not enough time; and beyond all of this all doctors, as all people, need personal time and a life outside work. Tell him that you are in no doubt that he is a very hardworking doctor.

6. Be honest about where you think performance falters

Explain that where you think this falters is in his desire to do everything, and now. Medicine, more than many jobs, requires many generic skills, and one of these is prioritisation. Explain that this is not a comment on his medical knowledge, which is perfectly satisfactory.

7. Identify problems and possible solutions

Explain that the transition from medical school to house officer means seeking and using the support of more senior staff. Perhaps explain that on your next ward round he should not leave unless a job is urgent, and that you and he can decide this together. Offer to supervise his work more closely, constructively correcting any problems and regularly teaching on ward rounds. Offer to meet at the end of shifts to see what work is remaining and, of this, what needs to be done now, what can wait and what should be handed over. Ensure that he is taking all leave to which he is entitled.

8. Invite further questions

Invite him to discuss anything not covered.

9. Agree a plan

Make and agree a definite plan, using the list of identified problems and possible solutions.

10. Offer ongoing help

Ensure he knows you will be an ongoing source of confidential help.

Discussion

Do you have a duty to identify poorly performing doctors?

Poorly performing doctors should be identified and supported in a proper manner. There should be a sense of responsibility for these doctors, even where performance is not considered abjectly dangerous because doctors are just as susceptible to personal problems and work difficulties as anyone else and need support rather than being left to languish in this and subsequent posts. Where patient care is considered to be at risk, these doctors should be identified with a view to further training or re-education, or other help as necessary. A plan for this should be constructed in a tailored way in conjunction with the consultant in charge and sometimes the postgraduate deanery. Re-appraisal will be necessary.

What types of problem doctor can you identify?

The General Medical Council (GMC) identifies the broad categories of poor performance (incompetence), misconduct (bad behaviour) and problems of physical or mental health (sickness), although each of these is of variable significance and often these overlap. It may be preferable to consider doctors as being in difficulty, often with a conspiring cluster of causes including personality type, behavioural predisposition and life events.

Is the problem usually of a doctor in difficulty or a difficult doctor?

It may be either.

Is the problem usually clinical or behavioural?

It is invariably behavioural. Complaints about doctors are usually to do with problems with attitude, communication, decision making, team working and insight. Behaviours may be:

- Work based, e.g. lateness, absence, work backlog
- Performance, e.g. over- or underinvestigating, poor decision making, poor record keeping, complaints
- Cognitive, e.g. memory, attention and learning problems
- Language / cultural
- Psychological/personal, e.g. irritability, unpredictability, forgetfulness, high self-criticism / perfectionism, arrogance, lack of insight, excess risk taking
- Social, e.g. isolation, withdrawal, poor personal interaction.

Stress is largely related to personality (degrees of openness, conscientiousness, extraversion, agreeableness, neuroticism), rather than work environment. The strongest predictors of success at work are emotional stability and resilience, conscientiousness and intelligence. A high degree of 'neuroticism' is less favourable. All behaviours may of course be strengths or weaknesses, e.g. diligence can be very productive or create impossible demands. Further, positive behaviours may become destructive if they go too far, which they may do under stress, e.g. enthusiasm becomes volatility, careful becomes too cautious, focused becomes passive aggressive, confident becomes arrogant, charming becomes manipulative, diligence becomes perfectionism.

What are the causes of poor performance?

These are wide ranging, e.g. poor knowledge or skills, difficulty putting theory into practice, arrogance or failure to know limitations (usually poor insight or overcompensated insecurity), poor communication, poor teamwork, offhand attitudes, laziness and dishonesty (almost undoubtedly the worst). Often one problem suggests that a cluster may be present. Interestingly, those who think they are good tend to overestimate themselves, and those who think they are not so good, underestimate! Good doctors can be bad doctors, e.g. the perfectionist who cannot delegate, and in general there are five working styles and we tend to each have a couple – 'hurry up', 'be strong', 'be perfect', 'try hard' or 'please people'.

What should be done when a doctor in difficulty is identified?

Early recognition is imperative. One of the worst repercussions of failure to take remediable action as soon as possible is a doctor who becomes alienated and loses allegiance to their team or organisation.

The principles with any poorly performing doctor are:

- Ensure patient safety – always the first question to answer (training is always a balance between patient safety and learning opportunity).
- Let the doctor know; too commonly he or she is the last to know.
- Be objective.
- Discover the cause (trainee, team or external factors?) – clarify concerns, identify contributing factors and assess the capacity to improve.
- Decide what action needs taking.

Action at your stage is to speak to your consultant. Further action depends on the problem, ranging from informal action to, at the other extreme, a formal hearing. The people who might become involved to help with trainees are the clinical and educational supervisor, the clinical tutor, and if ongoing or not resolvable the postgraduate dean and support services in the deanery, often in conjunction with the occupational health service if there are health issues contributing; sometimes the National Clinical Assessment Service (NCAS), an organisation which supervises doctors with performance or educational problems (often communication problems), acts on a strictly need-to-know basis with that doctor, retaining considerable confidentiality for the doctor. The NCAS mainly assists consultants and non-training grade doctors, largely aiming to support them through the problems and considering fitness for purpose, but it does get involved with some trainees.

List some duties of a doctor

The GMC advises that to maintain a good standard of practice and show respect for human life doctors should respect those duties listed in Box 4.41.

List some key components of good medical practice

The 2012 GMC guidance on good medical practice involves four domains (Box 4.42), updated from seven in 2006 – good clinical care, maintaining good medical practice,

Box 4.41 **Duties of a doctor**

Patients must be able to trust doctors with their lives and health. To justify that trust you must show respect for human life and you must:

- Make the care of your patient your first concern
- Protect and promote the health of patients and the public
- Provide a good standard of practice and care
- Keep your professional knowledge and skills up to date
- Recognise and work within the limits of your competence
- Work with colleagues in the ways that best serve patients' interests
- Treat patients as individuals and respect their dignity
- Treat patients politely and considerately
- Respect patients' right to confidentiality
- Work in partnership with patients
- Listen to patients and respond to their concerns and preferences
- Give patients the information they want or need in a way they can understand
- Respect patients' right to reach decisions with you about their treatment and care
- Support patients in caring for themselves to improve and maintain their health
- Be honest and open and act with integrity
- Act without delay if you have good reason to believe that you or a colleague may be putting patients at risk
- Never discriminate unfairly against patients or colleagues
- Never abuse your patients' trust in you or the public's trust in the profession

Box 4.42 **Good medical practice**

Domain 1: Knowledge, skills and performance

- Maintain your professional performance
- Apply knowledge and experience to practice
- Ensure that all documentation (including clinical records) formally recording your work is clear, accurate and legible

Domain 2: Safety and quality

- Contribute to and comply with systems to protect patients
- Respond to risks to safety
- Protect patients and colleagues from any risk posed by your health

Domain 3: Communication, partnership and teamwork

- Communicate effectively
- Work constructively with colleagues and delegate effectively
- Establish and maintain partnerships with patients

Domain 4: Maintaining trust

- Show respect for patients
- Treat patients and colleagues fairly and without discrimination
- Act with honesty and integrity
- Openness with legal/disciplinary procedures

teaching and training, relationships with patients, working with colleagues, probity and health.

A colleague is making small clinical errors. Who should be made aware?

This starts internally by involving your consultant. The colleague should be asked for his or her side of the story from the outset. Depending upon the level of concern, the matter might be referred to the lead clinician of your department, the clinical director, the medical director or the chief executive. It is also possible to report concerns anonymously to the National Patient Safety Agency, which can conduct a non-judgemental investigation.

CASE 4.42 FITNESS TO PRACTISE – MISCONDUCT IN A COLLEAGUE

Candidate information

Role

You are a doctor on an elderly care ward.

Please read this summary.

Scenario

Re: Dr Harry Winter, aged 28 years

Dr Winter, your new junior colleague, is developing a reputation as a rather arrogant doctor who wants to be an emergency physician. He has just come from the intensive therapy unit (ITU), where his advice to colleagues was either that their referred patients were too sick to come to ITU ('wouldn't survive anyway') or too well to warrant ITU and he seldom if ever took a patient. He has just rotated to working on your elderly care ward. One of your patients, an 84-year-old woman with a total anterior circulation stroke, developed aspiration pneumonia and was very distressed. While you were assessing her you asked that Dr Winter ensure that 5 mg of morphine be prepared and then administered to relieve her distress. He administered the injection and wrote up 5 mg on the drug chart. Later, the nurse told you that Dr Winter had asked her for 15 mg. She is sure that she made up 15 mg with him and it is documented accordingly on the controlled drugs record. You are aware that not infrequently larger doses of opiates are prepared than are used and the remnant amounts discarded. But this is not the first time the same issue has been noted with Dr Winter.

Your task is to discuss the incident with Dr Winter.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Dr Harry Winter is a competent and very confident doctor, so much so that he often feels his senior colleagues need to re-train. He has read a lot, knows a lot and gets very frustrated when senior colleagues waste time with what he sees as meaningless interventions and drug doses that do not seem to make a difference. He wants to be an emergency physician. He hates his current post on the elderly care ward, where things are too slow. In fact, he has contempt for most elderly care physicians, perceiving that a lot of resources are 'wasted' on older people who do not seem to get better. Yesterday, an 84-year-old woman with a total anterior circulation stroke developed aspiration pneumonia and was very distressed. While his senior colleague was assessing her he asked Dr Winter to ensure that 5 mg of morphine was prepared and administered. Dr Winter felt this dose stupidly low and had given much higher doses to young trauma patients in the emergency department. Dr Winter decided to give 15 mg and although the woman became extremely drowsy she is still alive today and this, he feels, vindicates his decision. He only prescribed 5 mg, however, knowing his senior colleague would not have approved. The nurse with whom he prepared the morphine challenged him about the discrepancy between what he had asked for and what he had prescribed. Dr Winter does not feel it is a nurse's place to question a doctor but to appease her said that he discarded 10 mg as it was subsequently not needed. This is not the first time he has given bigger doses than recommended or requested, but he feels he is right. The senior doctor now wishes to talk to Dr Winter about these episodes, and he will have to admit the truth, albeit exposing his contemptuous convictions, because the alternative is that he is perceived as taking the morphine himself, which he is not. In fact, he thinks drug addicts should be shot.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction and setting

Ensure you have time to talk with him, in a non-pressured environment, as much for your sake as his.

2. Open diplomatically

Tell him that you wish to discuss the discrepancy between the dose of morphine apparently administered and the dose given. Make it clear that you are not being judgemental, and that there are of course numerous potential reasons this could occur. You should be aware, however, that if he is lying about drug doses that will be a very serious issue of honesty and probity.

3. Make it clear you are there to offer constructive help

Explain that, whatever the motives, you would hope to be able to offer constructive help (it is of course more difficult to do this when a doctor with poor conduct does not seem to appreciate this).

4. Listen to the experiences of the doctor with poor conduct

Allow him to tell his story. Try to identify, if he admits to the act, his reasoning behind it and ask him if he saw any alternatives, such as discussing his thoughts with his senior colleagues first.

5. Share any good points

Acknowledge that he is generally a knowledgeable and competent doctor.

6. Be honest about where you think performance falters

Explain that you feel his ethical decision making is leading him into territory that is dangerous to patients and risking his professional integrity; explain that these actions could have very serious repercussions, not least threatening his future career.

7. Identify problems and possible solutions

With a lesser issue you might advise him that you would wish him to discuss all treatment decisions while attached to the elderly care ward with you. Tell him that medical decisions are always within a framework that puts patient safety first. Here, you must inform your consultant.

8. Invite further questions

Invite him to question your suggestions.

9. Agree a plan

Make and agree to a definite plan, using the list of identified problems and possible solutions. Tell him that the matter is not one that you can keep to yourself, and you will need to also discuss it with your consultant.

10. Offer ongoing help

Offer to be a source of advice and help during his attachment to the elderly care ward.

Discussion

What types of professional misconduct do we sometimes hear about in doctors?

These include (not in any order of importance):

- Lack of probity or honesty
- Lack of reliability and poor time keeping
- Acting under the influence of alcohol or drugs
- Inappropriate or criminal behaviour
- Inappropriate use of NHS facilities
- Failure to follow organisational policies
- Bullying
- Sexual or racial harassment
- Neglect of or disregard for responsibility to patients
- Breach of confidence
- Unprofessional attitudes to work.

What are the possible outcomes of challenges to a doctor's actions?

Possible outcomes are listed in Table 4.10. Your first duty is to speak to your consultant if you have concerns about

Table 4.10 Possible outcomes of challenges to a doctor's actions

Procedure	Who or what instigates	Who conducts	Purpose	Criteria	Possible outcomes
NHS complaints	Patients or relatives	Hospital managers or independent panel	To resolve complaints and improve service		Explanation or apology from managers
Negligence claim	Patients	Civil court with a judge	Compensation	'Bolam test'/prudent patient test	Financial compensation to patients
Employer's disciplinary proceedings	Reports from staff	Trust managers	Protection of patients	Breach of employment contract or law	Warning, suspension or dismissal
Professional bodies such as GMC	Health professionals	Professional committees	Assessing fitness to practise/public protection	Guidance such as GMC guidance	Admonition, registration with conditions, suspension from medical register or erasure from medical register
Criminal negligence	Crown Prosecution Service	Criminal court	Prosecution/punishment	Gross negligence	Absolute or conditional discharge, suspended imprisonment or imprisonment
Coroner's inquest	A reported death	Coroner	To determine cause of death		Verdict on cause of death

GMC, General Medical Council.

a doctor. Depending upon the seriousness of the problem, others involved include the Medical Director, the Chief Executive, the deanery and the General Medical Council. The police may be involved if there is criminal action. In the event of improper use of internet sites, trust IT departments may not inform the individual but have direct links to the police who will take it extremely seriously. Other people who may be involved in misconduct investigations are outlined in Table 4.10. Depending upon the action, restriction of practice or exclusion may ensue before investigations start. It is not acceptable to apply different outcomes to doctors as to other members of staff. If dismissal is appropriate for a porter, then it is for a doctor.

Should you accept a gift from a patient?

The general answer is no. Gifts that should not politely be returned, such as chocolates, might be shared with other members of the team; money should never be accepted and the patient might be advised to contact the Trust Patient Advice Service if they wish to make a charitable donation.

Should you always see a patient if a junior asks you to?

Patient safety comes first and if there are concerns about a junior's level of competence this should be handled second and your conduct in protecting patients will be paramount. You should see that patient.

CASE 4.43 FITNESS TO PRACTISE – HEALTH PROBLEMS IN A COLLEAGUE

Candidate information

Role

You are a doctor in the emergency medical admissions unit.

Please read this summary.

Scenario

Re: Dr Emma Wood, aged 26 years

Dr Wood, your new F1 doctor, has worked with you for 3 months and is persistently late for work. When at work, her performance is highly substandard. Notably, she is extremely slow, being able to clerk in one or two patients on days she is 'on take'. Initially, you gave her the benefit of the doubt as she told you she found work very stressful. She feels that doctors do not give enough time to patients, declaring that patients have 'emotional needs as well as physical'. But you now think this a thin excuse. She arrives at work smelling of alcohol, and colleagues have told you how she is often at parties all night or in her room with dubious friends drinking until an hour before work. On two occasions you have sent her home because she was intoxicated.

Your tasks are to confirm that she has an alcohol problem and find ways to manage the problem.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Dr Emma Wood has been an F1 doctor in medicine for 3 months. She was an average student, performing well in psychiatry, but finds being a doctor exceptionally difficult. Initially she found it a culture shock to have to see so many patients, and felt that most doctors did not spend enough time talking to their patients. She was told by one consultant that this is the modern NHS, there is a service commitment to see patients and it is better to 'get around all patients missing irrelevances' than to see one or two in depth. She found this infuriating and against what she found as a student in psychiatry, when she would frequently put in a whole afternoon talking with one patient. She now feels contempt for physicians. She cannot be bothered working with the team, which she thinks just runs around in circles, and feels she is 'destined for better things'. She has been drinking more and more alcohol in recent months – she always drank a lot as a student – and is aware that she comes to work after one or two morning drinks 'to steady her frustration' but does not think her colleagues have noticed. In any event, she enjoys it, and has increasingly been feeling that alcohol is a good thing for young people earning money and hates being criticised by people who tell her differently. Her senior is about to speak to her about his concerns, and she may eventually see that there could be a problem and agree to seek advice.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction and setting

Ensure you have time to talk with her, in a non-pressured environment, and make it clear that the discussion is confidential.

2. Ask if the sick doctor recognises the problem

Tell her that you are concerned she may be drinking heavily. Ask if she feels there may be a problem.

3. Make it clear you are there to offer constructive help

Explain that you are concerned and that you would like, and may need, to help or intervene if there is a problem.

4. Listen to the experiences of the doctor

Listen supportively, but be aware that she may not admit to having a problem. She may not see that she does.

Box 4.43 CAGE questions

- Have you ever felt you ought to **C**ut down your drinking?
- Have people **A**nnoyed you by criticising your drinking?
- Have you ever felt bad or **G**uilty about drinking?
- Have you ever had a drink first thing in the morning, an **E**ye opener?

5. Ask specific questions

Ask the CAGE questions (Box 4.43). Ask if anyone else has hinted that there may be a problem. Crucially, you are exploring whether or not she has insight into the problem. Explore the possibility of depression.

6. Be specific about your concerns

If she denies a problem, suggest the evidence. Explain you are concerned that continuing in this way may put patients at risk. Explain you are also very concerned about the possible implications for her, including not adequately making it through house year and, ultimately, a risk of not obtaining General Medical Council (GMC) registration. Explain that if patients are at risk she has a duty to seek help and if she does not then it is necessary for colleagues to intervene. Explain that you are obliged to speak to her consultant.

7. Explore any other concerns

Invite her to discuss anything not covered.

8. Discuss possible solutions

These include support from you, and help from her registered general practitioner and/or the occupational health service, and confidential services for sick doctors including the British Medical Association, the Sick Doctors' Trust and the Doctors' Support Network.

9. Agree a plan

Make and agree a definite plan.

10. Offer ongoing confidential help

Ensure she knows that you will be an ongoing source of confidential help.

Discussion

If you suspect a colleague's sickness is putting patients at risk, how do you decide when 'whistleblowing' overrides the confidentiality of the colleague?

You must protect patients from harm posed by another health-care professional's health, conduct or performance and this includes problems of alcohol or drug misuse. Patient safety comes first. Serious concerns should provoke immediate action to establish if they are well founded. You must give an honest explanation to an appropriate person in your health-care organisation, such as your consultant or the Medical Director. If local systems do not or cannot resolve the issue, then a professional organisation such as the GMC may need to be informed of your concerns.

If a colleague smells of alcohol and it is difficult to judge if he or she is drunk, and this is a first time, then it is more likely a case of local help and discipline with close observation. But any professional who smells of alcohol cannot see patients.

In recent years, gambling has also become a health-related concern.

In all cases, important considerations are:

- To alert the individual of your concerns
- To ensure patient safety, e.g. is immediate exclusion from work needed?
- To involve your consultant, who should act upwards depending upon the level of concern – Medical Director, Chief Executive, GMC
- The health of the individual, e.g. occupational health department.

CASE 4.44 RECRUITMENT TO A RANDOMISED CONTROLLED TRIAL

Candidate information

Role

You are a doctor on the acute medical unit.

Please read this summary.

Scenario

Re: Mr John Walker, aged 54 years

You are conducting a randomised controlled trial (RCT) with your consultant on inpatient insomnia. You have designed the RCT to involve four groups: no treatment, an eye-shield alone, earplugs alone, and an eye-shield plus earplugs. Patients will be randomised to one group for one night only and report their sleep satisfaction on the basis of a rating scale.

Your task is to ask Mr Walker, a patient admitted with dehydration and acute renal impairment, if he might agree to participate in the trial and counsel him about it.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Walker is a 54-year-old mathematician who has been admitted with acute renal impairment caused by gastroenteritis and dehydration. He is about to be asked if he might consider participating in a treatment trial, and will be very interested to know all about it, not least about the safety aspects and the ethics of it being conducted.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduce yourself and the topic for discussion

Explain that research is vital in improving the care of patients and that you would like to invite your patient to participate in research and the reason why. Ask if he is happy to discuss your project.

2. Explain the nature of the study

Explain the nature of the research, its aims and an outline of the method. For such a randomised controlled trial (RCT), the nature of the randomisation and any reasons for it should be explained, although by its very nature this RCT cannot be a double-blind RCT in which neither patient nor researcher know whether patient is receiving treatment or placebo.

3. Discuss ethics approval

Explain that ethics approval has been obtained and that the research does not come before the best interests of a patient and that there are legal rights and safeguards. Any foreseeable risks must never outweigh potential benefits and developing new knowledge or treatment should never take precedence over a patient's interests. An RCT is not ethical if there is evidence that an intervention is dangerous and an RCT must be stopped if evidence emerges for a benefit or risk before completion. Doctors involved in research have an ethical duty to respect human life and people's autonomy (if that research is an experimental study into the causes, treatment or prevention of disease, involving people or their tissues, organs or data; audit is not experimental study).

4. Explain potential benefits and risks

There may be potential benefits and risks. Explain these, and any arrangement for dealing with adverse events. Explain that the results are not predictable.

5. Explain data handling

Explain that you will record and report all results accurately. Explain that you will aim to complete the research unless evidence emerged of a risk or no potential benefit to participants. Information about outcomes will be available.

6. Discuss confidentiality

Explain that all information will fully respect your patient's right to confidentiality. Where data or patient information is needed for research, doctors must seek consent for its disclosure whenever practicable, anonymise data where this will suffice and keep all disclosures to the minimum necessary. If consent is not practicable, then the ethics committee may need to decide whether the likely benefits of the research outweigh the loss of confidentiality.

7. Discuss consent

If he would like to proceed then you would wish to obtain consent. Sometimes it is preferable to give patients time to think about things. On no account must a patient feel coercion. They also have the right to withdraw from research at any time without reason. Any additional information given, other than that required to fulfil a doctor's obligation to provide informed consent, will depend very much upon the individual. It should be determined by effective communication, by not making assumptions and by asking about specific concerns. An information leaflet is often very helpful before discussing research with patients.

8. Consider conflict of interest

Any conflict of interest should be declared from the outset and research should not be motivated by financial, personal, political or other interest. Ethics approval is mandatory.

9. Confirm understanding and invite questions

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Seek consent or refusal

And do not question his decision if he refuses.

Discussion

What do you understand by the term evidence-based medicine (EBM)?

EBM refers to the conscientious, explicit and judicious application of current best evidence in making decisions about the care of individual patients. Practising EBM must integrate external evidence with clinician's expertise and patient's beliefs, concerns, expectations, values and informed choice. Evidence-based health care extends the application of principles of EBM to all professions involved in health care.

What do you understand by the term critical reading or critical appraisal?

The ability to evaluate scientific literature, analyse data, and base management decisions on the evidence.

What broad types of research are there?

Quantitative research

This is concerned with inferences about populations and testing theories. A collection of numerical data is subject to statistical analysis to test hypotheses. Things that are measurable by quantitative studies include *disease frequency* (incidence and prevalence), *factors that modify risk of disease*, methods for *detection and diagnosis* of disease, *costs and consequences* of health states and *effects of treatments and interventions* (clinical trials).

Qualitative research

This is concerned with understanding the experiences of individuals and using this to build theories. It is guided not by hypotheses, but by questions and issues and seeks to describe culture, beliefs and attitudes and to understand behaviour. It may generate hypotheses for testing using survey or intervention designs. It may utilise, for example, case reports, interviews (structured and non-structured), health diaries, audio recordings, focus groups or group interviews.

What types of study design are there?

Study designs may be non-interventional (case reports, cross-sectional studies, case–control studies, cohort studies) or interventional, which measure 'before' and 'after' (RCTs, systematic reviews, meta-analyses). Study designs are listed below in the order of their ascending hierarchy of evidence.

Case report

This reports a single patient's story. A report on a series of patients with an outcome of interest is a case series.

Cross-sectional (descriptive) study

A representative sample of people ('subjects') is studied at a single point in time. It may be used to determine the prevalence of a particular disease. Subjects are selected without regard to the outcome of interest.

Case–control (retrospective) study

This involves identifying subjects with a particular condition of interest (*cases*) and comparing or 'matching' these with subjects without the condition of interest (*controls*). Retrospective data are collected from patient records to try to identify a past exposure or potential causal agent of interest that discriminates between the two groups. It is not possible to demonstrate causality from a case–control study; the association of A with B does not prove that A causes B. Subjects are selected based on the outcome of interest.

Cohort (prospective) study

This is an observational study of subjects without the condition of interest; they are selected and then followed up to monitor the occurrence of the outcome. Two or more groups (*cohorts*) are selected on the basis of a *difference in exposure to a particular agent of interest* (e.g. drug, potential toxin, smoking) and followed up to see how many in each group develop a *disease or other outcome*. Cohort studies may take years. A famous cohort study was that by Sir Richard Doll to investigate smoking as a risk factor for lung cancer. Subjects are selected before the outcome of interest is observed. It is not strictly possible to determine causality from a cohort study (something which tobacco companies have used in their defence in the face of overwhelming evidence) but strength of association may be used as a marker of risk. An RCT is needed to prove causality, but may not be ethical in the face of a strong association. Cohort studies may be used to determine prognosis.

Clinical trial

This is a planned experiment designed to assess the efficacy of a treatment in humans. The RCT is the most powerful experimental design to obtain evidence of causation or the impact of an intervention. Patients are randomly allocated or randomised into an experimental group to receive an intervention and a control group to receive standard treatment or placebo. These groups are followed up and compared for differences in outcomes of interest and any differences are tested for significance. The process of inference from an RCT will typically result in significance tests (P values), estimates of risk or treatment effect and confidence intervals (below). Advantages of an RCT include the rigorous evaluation of a single variable in a defined patient group, the prospective nature eliminating bias, the search to falsify rather than confirm its hypothesis and the facility for meta-analysis at a later date. Disadvantages include time and cost, hidden biases such as imperfect randomisation, funding sometimes by pharmaceutical companies, and the use sometimes of surrogate endpoints.

Systematic review and meta-analysis

A systematic review is a summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual valid studies and that uses appropriate statistical techniques to combine these studies. Meta-analyses pool data from numerous trials, and the Cochrane Collaboration is one body that has standardised this approach.

What is a clinical practice guideline?

A systematically developed statement designed to assist clinicians and patients in appropriate decision making.

Are there guidelines for critically appraising papers?

Checklists to assist critical appraisal have been developed for many different types of study and may include a clearly specified *objective*, a *design* appropriate for the objective, a definition of the *target population* and whether *generalisation* from the study to the target population is possible, *subject selection* (how the subjects were selected for inclusion), clearly defined *treatments/interventions*, whether *randomisation* was used for allocation (including treatment masking/blinding and if not whether this could affect outcomes), justification of the *sample size*, the *outcome measures* (primary and secondary, with statement of reliability and validity) and *completeness* (compliance, drop-outs or missing data). Checklists to assist critical appraisal have been developed specifically for RCTs. One such is the Consolidated Standards of Reporting Trials (CONSORT) checklist.

What is bias?

Bias refers to deviation of results from the truth, or processes leading to such deviation. *Selection bias* in a sample is an error caused by systematic differences between groups of subjects or between those selected and those who are not. For example, volunteers may differ from non-volunteers in health terms (motivated, free time, well). Selection should really be random. *Information bias* refers to a flaw in measurement that results in a difference in the quality of information between groups. There are many types of information bias:

- *Interobserver bias* resulting from different observers classifying outcomes
- *Recall bias* resulting from incomplete recall, worse in a case–control study
- *Lead-time bias*, important in measuring survival if a new procedure has been introduced (i.e. is an apparent increase in survival because of early intervention or a parallel diagnosis?)
- *Performance bias*, resulting from differences in care provided apart from the intervention (e.g. a doctor may or may not counsel as well as prescribing antidepressants)
- *Exclusion bias*, which implies systematic differences in trial withdrawals
- *Detection bias*, which implies a systematic difference in outcome assessment.

What information might you need to determine the sample size necessary for a study?

Sample size should be calculated by a statistician before embarking on a study. A larger sample may yield a more significant result. Sample sizes are determined from:

- An *estimation of prevalence* of the outcome of interest in the population being studied or the control group.
- *'Clinical intuition' to decide the minimal clinical difference* or smallest change in outcome between treatment and control groups that would be deemed clinically relevant.
- The *significance level*, which refers to the probability of a significant result, when in fact there is no difference. The smaller the better, but it could never be 0% unless we were to study the entire population. By convention the significance level is 5% or 0.05, represented as the '*P*' value (below).
- *Power*, which refers to the probability that a study of a given size statistically detects a real difference. The bigger the better, and the more likely to detect smaller differences, but power could never be 100% unless we were to study the entire population; 80% or 90% are by convention the standards.

What is the null hypothesis?

That there is no real difference between intervention and control (relative risk = 1 or absolute risk = 0). Trials start with this presumption, and then set out to disprove it. In other words, evidence is based on an innocent until proven guilty basis, a rather tortuous approach that requires a '*P*' value to be < 0.05 to be beyond reasonable doubt. We can never prove the null hypothesis, but only try very hard to reject it.

What is a '*P*' value?

The *P* value relates to the confidence that a difference between intervention and control groups is not the result of chance alone. Its value is arbitrary, and by convention < 0.05 (i.e. a < 0.05 or < 1 in 20 chance of the difference being due to chance alone) is deemed statistically significant. Sometimes tiers are considered, < 0.01 being yet stronger evidence and < 0.001 being very strong evidence. The smaller the *P* value, the less likely the difference is to be the result of chance alone and the more likely it is to be significant (but only if the sample size is large enough). A significant result suggests that the author reject the null hypothesis, and a non-significant result implies either no difference or too small a sample. The *P* value must always be read in the context of the sample size and confidence intervals. Formerly, *P* values were often given alone when reporting studies but, now, confidence intervals tend to be given also. Importantly, statistical significance need not necessarily imply practical, real or clinical significance. Furthermore, absence of evidence is not the same as evidence of absence!

What do you understand by the term confidence interval (CI)?

If we were to repeat a trial hundreds of times, we would not get the same results each time but on average we would establish a level of difference between the two arms of the trial. In 90% of the trials the difference between the two arms would lie within certain broad limits; 95% of the trials would lie within certain, even broader limits and 99% within broader limits still. *The CI is the range within which we would expect the true value of a statistical measure to lie. It is basically the degree of wobble in a result that is based on a small sample population (those in the study) rather than the entire population.* The CI is usually accompanied by the percentage value for the *level of confidence* that the true value lies within this range. For example, a number needed to treat (NNT; see Case 4.6) of 20 with a 95% CI of 15 to 25 implies that we are 95% confident that the true NNT is between 15 and 25. It is standard to have 95% CIs. CIs can be applied to any statistical test, e.g. NNT, relative risk, absolute risk, odds ratio, or sensitivity. A *P* value might be 0.05, but if, for the sake of example, the CI for that *P* value were 1.1 to 25 then the result could be of almost no significance because this CI is wide and 1.1 is close to the line of no significance. A wide difference in results (a wide CI), especially if close to or crossing the line of no significance, is less significant. A narrow difference in results (a narrow CI), distant from the line of no significance, is more significant. The line of no significance is 1 for ratios (negatives are not possible), such as relative risk or odds ratio, and 0 for absolutes, such as absolute risk.

What is a type 1 error?

The intervention is shown to work but it does not! This is equivalent to the *P* value.

What is a type 2 error?

The intervention is shown not to work but it does! This is more common than a type 1 error.

What do you understand by the term generalisation?

Making inferences from a clinical trial involves a process of generalisation from the sample to the target population. The extent to which this is appropriate is known as generalisability.

What do you understand by the term confounding factors?

Mixing of two or more factors so that their individual effect upon an outcome cannot be separated.

What do you know about intention to treat (ITT) analysis?

Drop-outs or non-respondents can alter a sample size and conclusions significantly. ITT is an analysis in which the results in the control and treatment groups are analysed with respect to the numbers of patients entering the study (regardless of whether or not they received treatment or completed participation in the RCT). By including for analysis all entrants to the study, ITT analysis avoids biases because of a failure of concordance and admits side effects of a treatment causing subjects to drop out. ITT analysis provides a pragmatic estimate of the overall benefit of intervention in the population studied.

Other communication, ethical and legal scenarios

CASE 4.45 GENETIC TESTING

Candidate information

Role

You are a doctor on the neurology ward.

Please read this summary.

Scenario

Mr Roger Molton, aged 58 years

Mr Molton was recently admitted to the neurology ward for assessment of a movement disorder. Genetic testing has recently confirmed Huntington's disease and you are about to speak to his son, who wants to know more about the condition, particularly whether or not it is inherited and whether or not he and his siblings should be tested.

Your task is to explain the diagnosis and counsel him about testing for this condition.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

You are the son of Mr Roger Molton, a 58-year-old man who has recently been diagnosed with Huntington's disease. You know a little about the effects of the disease and have heard that it might be inherited. You wish to discuss the likelihood of being affected and if there is a test that you could have. You currently have no children but are concerned about the possible risk of passing the condition on to any children in future.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and establish his identity.

2. Establish area for discussion and background knowledge

Discover his pre-existing knowledge of Huntington's disease.

3. Establish any family history

Try to obtain a family tree and ask if he knows of anybody in the family who has had similar symptoms.

4. Explore ideas, concerns and expectations

Ask if he wishes to know anything else about the disease or its implications.

5. Respond to ideas, concerns and expectations

Explain that Huntington's disease is caused by an abnormal gene that is passed on to 50% of children. Explain that the disease may not become apparent until later life in affected offspring, but that there is a tendency for successive generations to be affected at an earlier age. Explain that offspring who do not carry the gene cannot ever be affected or pass on the condition.

6. Advise about genetic testing

Explain that genetic testing can determine whether he carries the abnormal gene. Explain that false-positive and false-negative tests do occur, but are very unusual. Point out that there are potential medical, family, occupational, insurance and financial implications of a positive result. Point out that there is no current prevention or cure for those carrying the gene. Point out that for those carrying the gene there is no means of predicting age of onset of symptoms, severity of symptoms or rate of progression.

7. Advise about counselling for genetic testing

All doctors should have a grasp of the principles and be able to respond to immediate questions and concerns. However, counselling for genetic testing is a specialised skill and counsellors should be specifically trained and part of a multidisciplinary team with psychosocial support. Having confirmed his understanding of Huntington's disease, explored and responded to his concerns, and explained the nature of testing, advise that a decision about the test is something he should not make now, but consider discussing with those close to him. Advise that he might discuss the implications of the test and the condition further at a regional genetic centre if he wished, and in the company of someone close to him, but at the very least your neurology consultant should be involved in the process. A minimum of 1 month is desirable between initial pre-test information and testing and results should always be given in person by the counsellor. Post-test counselling is mandatory whatever the result.

8. Consider legal aspects

As with human immunodeficiency virus testing, testing for Huntington's disease should never be performed without counselling and explicit informed consent. Counselling must include up-to-date information about the condition and the implications of testing that allow a patient to make an informed choice. The test is available only to those who have reached the age of maturity. Ownership of the test result is with the subject who requested it but ownership of the stored DNA is with the patient. DNA from another affected family member may be needed, who of course must give consent, but asking an affected family member who is unaware of or unwilling to acknowledge their symptoms may be considered an invasion of privacy. Care should be taken when a test result may provide information about a third party who has not requested a test. Oral and written information should be provided by the team providing the testing service.

9. Invite questions

Ask if he has any other questions or concerns that have not been addressed.

10. Agree a way forward

This may well be for him to think about the above before contemplating the next steps.

Discussion

What is Huntington's disease?

Huntington's disease is an inherited neurodegenerative disease characterised by progressive motor, cognitive and psychiatric symptoms. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes first. The disease is most common in people of northern European origin. The mean age of onset of symptoms is 40 years, but juvenile onset (< 20 years) and older onset (> 70 years) forms are well recognised. Although relatively uncommon, Huntington's disease can be devastating for patients and their families. People who are at risk of developing the disease because of a family history face difficult decisions about genetic testing.

What are the clinical features of Huntington's disease?

The disease was originally named Huntington's chorea after George Huntington, who wrote the first detailed description in 1872. The name has changed to Huntington's disease to reflect the fact that chorea is not the only important manifestation. Huntington's disease progresses over 15–20 years and characteristic symptoms reflect a triad of motor, cognitive and psychiatric manifestations.

- Motor symptoms can be divided into two categories: added involuntary movements such as chorea and impaired voluntary movements, which cause limb incoordination and impaired hand function. These symptoms are worsened by loss of postural reflexes. The pattern of symptoms tends to change over time, with chorea declining and dystonia, rigidity and bradykinesia becoming more marked.
- Cognitive impairment includes slowing of thought processing and deterioration of executive functions (high-level cognitive processes that control other aspects of cognitive function). Typically, patients report difficulty with multitasking, concentration and short-term memory. Thinking style becomes more concrete and less efficient, and the planning, initiation and organisation of time, thoughts and activities become harder. People with Huntington's disease are often impulsive and develop psychomotor perseveration. Visuospatial perception can also deteriorate
- Psychiatric symptoms include depression, obsessive–compulsive disorders, anxiety, irritability, apathy, hypersexuality (uncommon) and psychosis (uncommon). Suicide is not uncommon.

What is the genetic basis of Huntington's disease?

Huntington's disease is a single gene disease with autosomal dominant inheritance. The genetic abnormality is an expanded CAG trinucleotide repeat within the huntingtin (*HTT*) gene on chromosome 4, and it can be identified through genetic testing. The *HTT* gene encodes the protein huntingtin, essential for normal neural development, although its functions are incompletely understood. In Huntington's disease the expanded *HTT* gene encodes a mutant form of huntingtin protein, which leads to the development of Huntington's disease through many pathogenic mechanisms. Offspring of an affected parent have a 50% chance of inheriting the genetic abnormality, and males and females are affected equally. Huntington's disease does not skip generations.

How is genetic testing undertaken?

Genetic testing for Huntington's disease is performed by measuring the CAG repeat length in the *HTT* gene. A 'positive' test result refers to CAG lengths in the pathogenic fully penetrant CAG repeat range of more than 39 repeats. Testing falls into two categories.

- Diagnostic testing is carried out to confirm (or refute) the diagnosis in a patient with symptoms suggestive of Huntington's disease. It is a test for manifest disease and is most commonly undertaken by neurologists. A positive diagnosis has numerous implications for family members (especially children and siblings) and for the patient.
- Predictive testing is carried out in a person who has no symptoms of the disease, but who is at risk because of their family history. It determines whether that person carries the expanded *HTT* gene and will develop Huntington's disease in the future. A positive predictive test result indicates that they will certainly develop Huntington's disease at some point if they do not die from something else.

What ethical considerations surround genetic testing?

Confidentiality and consent

Strict confidentiality is observed before, during and after predictive testing. Written informed consent must be obtained from the patient before either predictive testing or diagnostic testing. If the patient lacks capacity to make the decision him- or herself for diagnostic testing, consent can be given by an authorised representative.

Having children

Deciding whether or not to have children is often difficult for people with or at risk of having an expanded *HTT* gene and is outside the scope of this text.

What are the implications of a positive gene test?

There are major emotional and practical implications and testing and counselling should be undertaken by experts in the condition.

How is Huntington's disease managed?

The aim of treatment is to manage symptoms and improve quality of life. No current treatments can slow disease progression. The choice of drugs for symptom relief is based largely on clinical experience rather than evidence. Tetrabenazine has the best evidence of efficacy in Huntington's disease and has been shown to reduce chorea. Many non-drug measures are effective, within a multidisciplinary approach. Planning for end-of-life care raises several ethical problems often relating to how far medical interventions should be pursued when patients no longer have capacity to make their wishes known. Advanced decisions to refuse treatment can be extremely helpful. As Huntington's disease progresses, it often becomes increasingly difficult to provide care at home, and a nursing home may be needed. Insertion of a gastrostomy tube may be appropriate in patients who are unable to maintain adequate nutrition, depending upon extent of disease and pre-emptive information and wishes.

CASE 4.46 HIV TESTING

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

> Re: Mr Julian Lyons, aged 36 years
>
> Mr Lyons is a 36-year-old ex-intravenous drug user, who has abstained from drugs for 3 years. He has been admitted to your ward with a respiratory illness, mild hypoxia and X-ray findings that would be consistent with *Pneumocystis jirovecil* pneumonia. He has also been losing weight. Your consultant has asked that you discuss an a human immunodeficiency virus (HIV) test with him.
>
> Your tasks are to explain the possible diagnosis, approach the possibility of HIV infection and counsel him for an HIV test.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Julian Lyons is a 36-year-old man who used intravenous heroin until 3 years ago. He admits to having shared needles. He has been admitted to hospital with a short respiratory illness and his doctors suspect human immunodeficiency virus (HIV) infection as a possible underlying cause. He has been slowly losing weight over the last few months. He is heterosexual, currently unemployed, and lives with a dog. He smokes 20 cigarettes a day and drinks a moderate amount of alcohol. He has never had an HIV test. The possibility of HIV has crossed his mind and he is willing to undergo an HIV test but first would like to know more about implications of the test.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself, confirm his identity and ask how he is.

2. Explain the results of tests

Explain that the chest X-ray suggests pneumonia, and that there are a number of possibilities underlying it.

3. Explore risk factors, suggesting possible implications of the results

Ask about his heroin use. Did he share needles? Were any of his associates known to be HIV positive? When did he stop using intravenous drugs? Ask about other risk factors for HIV acquisition, especially the sexual history. These questions suggest that HIV is on your mind and if he does not respond suggest that HIV is something that must always be considered.

4. Explore ideas, concerns and expectations

Ask him if this is something that has crossed his mind, or if he has ever considered the possibility of HIV infection.

5. Respond to ideas, concerns and expectations

Explain what HIV and acquired immunodeficiency syndrome (AIDS) are, and how HIV is transmitted (and how transmission can be reduced).

6. Counsel with respect to HIV testing

Pre-test counselling should prepare an individual for receiving, understanding and managing a result. Discussion should embrace the consequences of a positive result, including impact on partners, pregnancy, employment and insurance (Box 4.44).

7. Give an assurance of confidentiality

This is essential.

8. Invite questions

Ask if he has any other questions or concerns that have not been addressed.

9. Seek consent to proceed with the HIV test

Agree that he should decide whether or not to go ahead with the test, and if he goes ahead who will inform him of and explain the result, and that you will continue to investigate and treat his pneumonia.

Box 4.44 **Counselling with respect to human immunodeficiency virus (HIV) testing**

- Ask if he has ever had an HIV test.
- Ask if he would consider one, reassuring him that the test is entirely confidential. Emphasise that it is a test for the presence of HIV, and not an 'AIDS test'.
- Explain how the test is performed – a simple blood test, the result usually available the next day.
- Ask what impact he suspects a positive result would have on him.
- Emphasise the benefits of the test (early treatment, knowledge of infectivity to others).
- Ascertain if he has a regular sexual partner. Explain that, if positive, it would be essential to tell his partner and desirable that his general practitioner be informed. He may ask whether life assurance policies would be affected. Generally, if negative, individuals are not discriminated against. If positive, all previous policies should be honoured, provided all relevant information was faithfully disclosed at the time. Future policies may be difficult take out.
- He may ask if he has acquired immunodeficiency syndrome (AIDS). Explain that the test is for HIV, but that if positive and tests confirm *Pneumocystis* pneumonia, then that is an AIDS-defining illness. Tell him that he does not have to decide immediately as to whether or not to proceed, but you will continue investigating and treating his pneumonia.

10. Discuss what would happen after the test

Post-test counselling is mandatory, whether a positive or negative result, and the pre- and post-test counsellor should really be the same person.

Discussion

Does a negative test exclude HIV infection?

No. The window period means that testing must be repeated if there is a possibility that infection has been acquired in the last few months. The management of HIV infection is further discussed in Case 2.39.

CASE 4.47 NEEDLESTICK INJURY

Candidate information

Role

You are a doctor in the emergency medical admissions unit.

Please read this summary.

Scenario

Re: Dr Tess Martin, aged 25 years

Dr Martin is an F1 doctor (house officer) working with you. She comes to you extremely upset because she has sustained a needlestick injury while taking blood from a patient she has just clerked, who is an intravenous drug user.

Your tasks are to calm the situation and advise about managing the needlestick injury.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Dr Tess Martin is an F1 doctor (house officer) working on the emergency medical admissions unit with her senior (the candidate). She has just sustained a needlestick injury from a patient who is a known intravenous drug user, admitted with a soft-tissue infection. The patient told her that tests for human immunodeficiency virus (HIV) and hepatitis 2 years previously were negative, but that his status had not been checked since and he has continued to use intravenous drugs. Dr Martin wore two pairs of gloves for the procedure. After withdrawing the green needle it punctured her gloves and 'pricked the end' of her left index finger, drawing blood. She immediately, quite correctly, washed the area with soap and water without scrubbing, and allowed the injury site to bleed freely. She is not sure about the risks of HIV and hepatitis C in this situation, nor what she should do next. She is fully immunised against hepatitis B with an excellent antibody response.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Ask Dr Martin exactly what happened and reassure her that you will help and follow the hospital guidelines for dealing with a needlestick injury.

2. Advise on immediate management

Advise her to wash the contaminated area thoroughly and allow the wound to bleed freely (if she has not already done so).

3. Establish details of the incident

Establish the nature of the injury, the type of needle used and the time of the incident.

4. Establish details about the patient and the staff member

Establish whether HIV and hepatitis B and C status are known. Ask if Dr Martin has been immunised against hepatitis B.

5. Remain calm

Explain immediately that the risk of infectious disease transmission is not all that high from a positive patient, and that she has acted quite correctly so far to reduce any risk even further.

6. Explain what you will do next

Explain that you will counsel and take a blood sample from the patient for HIV and hepatitis B and C (this should not be done by the individual who was exposed). Explain to Dr Martin that she should be encouraged to have a blood test also for HIV and hepatitis B and C and offer to counsel her to do this (or, as is common these days, these duties are performed by the emergency department staff, who will arrange counselling and testing of patient and staff member for baseline bloods and repeat testing of staff member 3 months later; if the patient lacks capacity blood may be taken and stored).

7. Respect confidentiality and consent

Assure her of confidentiality. Advise that, without a test now, if she were later found to be positive it might be difficult to claim compensation (industrial disablement benefit). Confidentiality for both parties is essential and of course counselling and consent for HIV testing are mandatory.

8. Explore outstanding concerns

Explore any other concerns she may have or if there is anything she is not sure about.

9. Invite questions

Ask if she has any other questions.

10. Consider the remainder of the shift

Suggest that she might wish to go off duty and that you will arrange the necessary cover.

Discussion

What is the risk of HIV transmission from a positive patient following needlestick injury?

Around 0.3%, but individual risk depends upon the nature of the inoculation and viral load transmitted, together with the HIV subtype and immunological factors in the person sustaining the injury.

What action is indicated in the setting of needlestick injury if a patient is known to be positive for HIV?

Action points are listed in Box 4.45.

What factors increase the risk of occupationally acquired HIV transmission?

These include deep injury, visible blood on the device causing the injury, injury with a needle that has been inserted in the source patient's vein or artery and terminal HIV-related illness in the source patient.

Box 4.45 Action for needlestick injury from a human immunodeficiency virus (HIV) infected individual

- An anti-HIV triple therapy starter pack should be given within the first hour. The occupational health department can advise on up-to-date local guidelines (national guidelines have been developed on post-exposure prophylaxis for health-care workers by the Chief Medical Officer's Expert Advisory Group on AIDS), and if outside normal working hours the hospital senior nurse should know where the latest guidelines are and where treatments are kept.
- Health-care workers exposed to infectious patients should be given the opportunity to discuss the balance of risks with appropriate psychological support, particularly allowing informed decisions about post-exposure prophylaxis.
- Post-exposure prophylaxis employs combination therapy for 4 weeks.
- Pending follow-up and absence of seroconversion, health-care workers need not modify their work.
- All exposed individuals should be given advice on safe sex and avoiding blood donation.
- Follow-up is through the occupational health department and HIV retesting is performed at 6 months.

Would your management be any different if your house officer were pregnant?

She should tell her obstetric consultant of the incident, and this is essential if the incident involves an infected patient. Zidovudine and lamivudine are considered safe in the second and third trimesters of pregnancy but experience with other treatments is limited. However, the advantages are generally deemed to outweigh the risks and reduce the risk of vertical transmission.

CASE 4.48 MEDICAL OPINION ON FITNESS FOR ANAESTHESIA

Candidate information

Role

You are a doctor on the medical ward.

Please read this summary.

Scenario

Re: Mrs Beth Evans, aged 80 years

Mrs Evans was admitted to hospital 10 days ago under the care of the orthopaedic surgeons following a fractured neck of femur. On admission her course was complicated by right lower lobe pneumonia from which she is recovering well on your ward. Her past medical history includes osteoporosis, ischaemic heart disease and heart failure and current medications are antibiotics, aspirin, furosemide, a nitrate spray and topical hormone replacement therapy. Blood pressure is currently 160/90, heart sounds are normal with no added sounds or murmurs and there are bibasal crackles. Renal function and blood haemato-biochemistry are normal, and her total cholesterol is 5.6 mmol/l.

Your task is to assess the lady's medical condition with a view to whether she might undergo hip surgery.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Beth Evans is an 80-year-old widow, hitherto living alone in a bungalow. She was admitted to hospital 10 days ago following a fall on her steps (there are three steps up to the front door of her bungalow). She has fractured her left neck of femur and this requires surgery. Surgery has, however, been postponed so far because of pneumonia, confirmed when she came into hospital. This has been treated successfully, and now the orthopaedic team would like a medical assessment, mostly to see whether Mrs Everdene is fit to undergo surgery. Her past medical history comprises osteoporosis confirmed by a bone densitometry scan, angina (only on exertion) and heart failure, and her medications are aspirin, furosemide and a nitrate spray. She also takes a hormone replacement patch, and has done for 20 years, as it relieves hot flushes and she was once told that it helped osteoporosis. Her general practitioner once suggested stopping it but she does not think 'she could live without it'. Mrs Evans will accept the opinion of the medical team as to whether she is yet fit for surgery but is worried about her heart and will ask the doctor for an honest view.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself, confirm her identity and ask how she is.

2. Clarify the task

Explain that you are a physician and are here to advise on her medical problems and help optimise her treatment before any operation. Explain that you are not the anaesthetist, who would be responsible for deciding whether or not she is fit for an anaesthetic.

3. Explore symptoms

Explore the symptoms of ischaemic heart disease and heart failure and how these may limit her and what medications she has taken in the past.

4. Explore the past medical history

Explore the history of osteoporosis, how it was first diagnosed (e.g. previous fractures, strong family history of osteoporosis or fractures) and enquire about the hormone replacement therapy – how long she has been on it, and for what reason (osteoporosis, symptoms of oestrogen deficiency such as flushes). Ask about other medical problems or medications. Ask about previous operations and anaesthesia. Ask about any allergies.

5. *Explore ideas, concerns and expectations*

Explore any concerns she may have about her medical problems or the operation.

6. *Explain and advise as clearly as possible*

Suggest that you would like to examine her, especially her heart and lungs, and review the electrocardiogram (ECG) and chest X-ray. Suggest that you may recommend optimising treatment of her problems, notably with a view to reducing the future risk of heart attacks and fluid on the lungs. Ask if she is willing for you to adjust her medication regimen, and that the adjustments will probably include adding in a drug known as an 'ACE inhibitor' (beware preoperatively) and a statin (to reduce cholesterol and stabilise endothelium) and possibly another diuretic (spironolactone). A beta blocker may be considered later. An echocardiogram would be useful. Explore the past diagnosis of osteoporosis (presumptive or confirmed by bone densitometry) and the reason for her taking hormone replacement therapy (osteoporosis or symptoms of oestrogen deficiency such as flushes and atrophic vaginitis). Suggest that you would strongly advise the hormone replacement therapy being withdrawn, as the risks (venous thromboembolism, arterial disease, breast cancer) now very much outweigh any potential benefits (osteoporosis prophylaxis) and that there are now better treatments for osteoporosis than hormone replacement therapy (a bisphosphonate with calcium and vitamin D supplementation).

7. *Repeat important information*

This can be an effective way of emphasising 'take home' messages.'

8. *Confirm understanding*

Ensure that she understands your advice.

9. *Encourage feedback and invite questions*

> I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. *Agree a way forward*

Physicians are frequently asked to give an opinion on whether or not a patient is 'fit for surgery' or 'fit for anaesthesia', and the crucial decisions as to whether the patient would tolerate anaesthesia and the appropriate mode of anaesthesia must be made by an anaesthetist. Explain to patients (and the team making such a request) that you are not an expert in anaesthesia or the right person to judge anaesthetic fitness, but that you are delighted to advise on optimising medical care. Your role is to give a medical opinion that can be used to optimise a patient's health prior to surgery.

Discussion

List some risk factors for anaesthesia

Age is an independent risk factor (a strong predictor for adverse cardiorespiratory outcomes such as arrhythmias, hypotension and death) but anaesthetists look more closely at factors such as comorbidity, obesity, reflux and a difficult airway. Exercise tolerance in daily life reflects biological age and functional status can be measured in metabolic equivalents or METs (Table 4.11): 1 MET corresponds to oxygen consumption of 3.5 ml/kg/min (70 kg 40-year-old man at rest). Excellent functional reserve is > 7, moderate 4–7 and poor < 4 (Table 4.11).

Why are surgery and anaesthesia such a threat?

Surgery causes blood loss and fluid shifts. Post-operatively surgery causes pain (with reduced coughing and increased risk of respiratory infection), limits movement and triggers the stress response of sympathetic activity, glucocorticoid activity and fluid and salt retention. There is also reduced enteral absorption, altered immune function and altered coagulation. These changes peak in the first 2 days but linger for weeks.

Most intravenous anaesthetic drugs have adverse cardiovascular effects, reducing afterload and having negative ionotropic effects. They cause apnoea necessitating positive pressure ventilation and inhibit mucociliary function for 24 hours. They adversely affect renal function. Propofol, an induction agent, reduces systolic pressure by 40% on average in elderly patients. Regional anaesthesia vasodilates the affected area and interrupts sympathetic innervation of the heart and can result in marked bradycardia and hypotension if near the higher thoracic outflow.

Anaesthesia affects thermoregulation. A drop of 2°C centrally in the first 20 minutes is normal but can take an hour or two to recover with active warming. This hypothermia has a profound effect on cardiorespiratory, cerebral, clotting and immune function.

What cardiovascular problems are provoked by anaesthesia?

Increased arterial stiffness with age increases afterload such that there is little change in cardiac output with an

Table 4.11 Exercise tolerance measured in metabolic equivalents (METs)

MET	Activity
1	Self-care Using toilet Walking at 2–3 mph
4	Light housework Climbing a flight of stairs or a hill Walking at 4 mph Running a short distance
> 10	Dancing, golf Highly strenuous sports – swimming, football

increase in as the left-ventriclar end-diastolic volume increases. Consequently:

- Atrial systole is even more important in situations where it is less likely (!) and anaesthetists do not like to anaesthetise patients with fast or variably controlled atrial fibrillation except in emergencies.
- Reduced diastolic time reduces coronary flow and ST changes on the ECG are common, especially at induction. These changes, often associated with hypotension and tachycardia, may respond to fluid challenges but the sting in the tail is that elderly patients are less tolerant of this.

Post-operative myocardial ischaemia remains the biggest cause of death and morbidity in elderly patients. Myocardial infarction tends (anecdotally) to occur on the second post-operative night. Systolic murmurs are extremely common. A good exercise tolerance and ECG are usually reassuring pre-operatively, but significant aortic stenosis combined with anaesthesia can lead to a disastrous drop in afterload. Heart failure does not blend well with anaesthesia for all of the reasons outlined.

Is hypertension a risk factor for anaesthesia?

For every 10 mmHg in systolic pressure above 140, there is an odds ratio of 1.2, such that a systolic pressure of 180 doubles the risk of infarction.

What medical problems are relevant to anaesthesia?

Other important problems include respiratory problems with reduced functional residual capacity or low oxygen saturation (higher inspired oxygen is needed and positive pressure ventilation increases ventilation/perfusion mismatch), respiratory tract infection, reflux, confusion, alcohol misuse, electrolyte disturbance, obesity, hypothyroidism and drugs.

CASE 4.49 FITNESS TO DRIVE

Candidate information

Role

You are a doctor in the diabetes clinic.

Please read this summary.

Scenario

Re: Mrs Julie Blyth, aged 36 years

Mrs Blyth has type 1 diabetes and takes insulin. She has problems with hypoglycaemic unawareness. She is still driving and you are immediately concerned by this.

Your task is to explore the issue of driving with her and make some recommendations.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mrs Julie Blyth is a 36-year-old single mother of three children. She has type 1 diabetes and takes the combination of long- and short-acting analogues glargine and Novorapid respectively. She is very afraid of long-term diabetes complications and runs her blood glucoses very tightly between 3 and 4 mmol/l, which she believes to be the normal range. She has frequent hypoglycaemic symptoms (sweats, light-headedness), but does not recognise these as such. She feels she must drive. She drives a car to pick her children up from school and a small delivery van for an income. She is very concerned that the doctor in the diabetes clinic could 'take her licence away.'

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and confirm her identity.

2. Provide initial reassurance

Reassure her that you wish to try to establish why she is having symptoms and aim to correct these, rather than recommend that she does not drive.

3. Review her diabetes treatment and any complications to date

Be aware that insulin is a contraindication only to driving a heavy goods vehicle and not to other driving provided she is not having hypoglycaemic episodes.

4. Be alert to ideas, concerns and expectations

Establish the discrepancy between her idea of normal blood glucose readings and what is in fact normal.

5. Reframe her ideas

Explain that she should be aiming for a blood glucose reading of 4–7 mmol/l, and that she is currently aiming too low and this is likely to be giving rise to symptoms. Reassure her that resetting her target should not increase her risk of long-term complications.

6. Keep it clear

Keep your explanation as clear as possible.

7. Repeat important information

If she is anxious this may be especially important.

8. Confirm understanding

Ensure that she understands that her blood glucose target was too low.

9. Encourage feedback and invite questions

I appreciate we've covered rather a lot there. Is there anything you would like me to go over again or are there any questions you would like to ask me?

10. Agree a way forward

Assure her that she will be able to drive, but only when her blood glucoses are normal. Ensure that there are arrangements for treatment and follow-up.

Discussion

Who is legally responsible for deciding whether a patient is unfit to drive?

The Driver and Vehicle Licensing Agency (DVLA) is responsible. The DVLA should be informed if a patient who holds a driving licence has a medical condition that now or at some future date may affect driving safety. The legal basis of fitness to drive lies in the Road Traffic Act of 1988 and subsequent regulations

When might it be a doctor's responsibility to inform the DVLA?

These are outlined in Box 4.46.

Do you know the differences between a prescribed disability, a relevant disability and a prospective disability?

- A prescribed disability is condition that legally bars the holding of a driving licence unless certain conditions are met, e.g. epilepsy.
- A relevant disability is a condition that probably renders a person unsafe to drive, e.g. visual field defect.
- A prospective disability is a progressive or intermittent condition that may in future lead to a relevant or prescribed disability, e.g. type 1 diabetes.

Box 4.46 **Situations when a doctor might need to inform the Driver and Vehicle Licensing Agency (DVLA)**

- If a patient lacks capacity to understand advice not to drive, e.g. dementia.
- If a doctor is aware that a patient continues to drive against medical advice, every reasonable step may be made to persuade the patient to stop, and this may include breaching confidentially and speaking with a relative. If a doctor is unable to persuade, or becomes aware that such a patient is continuing to drive, then the relevant medical information should be disclosed immediately to a medical adviser at the DVLA. Before disclosure, a patient should be informed of the decision to do so, and afterwards informed by letter. The patient's general practitioner should also be informed.

May a patient with a prospective disability drive?

Yes, subject to medical review at defined intervals.

What are the visual requirements for driving?

The visual acuity requirement for driving a private car is based on the number plate test. A person should be able to read in good light a number plate of letters or numbers 79.4 mm high (binocular vision with correction for any refractive error) at 20.5 m. This equates to a visual acuity of between 6/9 and 6/12 on a Snellen chart. Failing to meet the requirement constitutes a prescribed disability and a licence must be refused or revoked. The minimum field of vision for safe driving is at least 120° on the horizontal measured by the Goldmann perimeter.

What are the rules on driving after a seizure?

Current legal rules for drivers (of non-heavy goods or public transport vehicles) are that they must be seizure free for more than 12 months or free of daytime seizures for more than 3 years if seizures are purely nocturnal. These rules apply on or off anti-epileptic drugs. Patients must not drive for 6 months following any dose adjustment. Patients have a legal duty to inform the DVLA of their condition.

CASE 4.50 INDUSTRIAL INJURY BENEFITS

Candidate information

Role

You are a doctor in the respiratory clinic.

Please read this summary.

Scenario

Re: Mr Andrew Hopkins, aged 77 years

Mr Hopkins is a retired shipyard worker, and has been progressively breathless. His chest X-ray suggests pulmonary fibrosis and there is pleural thickening with calcified pleural plaques. Pulmonary function tests reveal moderate restrictive lung disease and a thoracic computed tomography scan confirms interstitial lung disease. All of this suggests asbestos-related lung disease. Mr Hopkins is here for results and says that a friend told him he might claim industrial disablement benefit were asbestos the cause.

Your task is to explain the results and discuss the way forward for industrial disablement benefit.

Your examiners will warn you when 12 minutes have elapsed. You have 14 minutes to communicate with the patient/subject followed by 1 minute of reflection. There will then follow 5 minutes of discussion with the examiners. Do not take the history again except for details that will help in your discussion with the patient/subject. You are not required to examine the patient/subject.

Patient/subject information

Mr Andrew Hopkins is a 77-year-old retired shipyard worker, exposed to asbestos for at least 25 years of his working life during handling of construction materials. He has been progressively breathless over the last 18 months and a chest X-ray, pulmonary function tests and thoracic computed tomography scan have confirmed asbestos-related lung disease. He is aware that industrial disablement benefit is available from the Department of Social Security (DSS) and wishes to discuss this.

How to approach the case

Communication skills (conduct of interview, exploration and problem negotiation) and ethics and law

1. Introduction

Introduce yourself and ask how he is.

2. Explain the results of tests

Explain that there is thickening of the lining of the lungs with plaques (hard patches) due to asbestos exposure, and also scarring of the lungs almost certainly due to asbestos (asbestosis).

3. Explore occupational history

Obtain details of different occupations and length of exposure with each.

4. Explain the implications of the results

Explain that treatment options are limited and that asbestosis tends to progress, albeit slowly, but reassure him that there is no evidence of lung cancer or cancer to the lining of the lung (mesothelioma) which can occur in asbestos lung disease.

5. Establish knowledge of eligibility for compensation

Ask if he aware of his eligibility to claim for industrial disablement benefit.

6. Explain the legal position

Explain that people with asbestos lung disease are entitled to compensation. Explain that a DSS medical officer would visit to assess the degree of disability and that this information would help determine the level of benefit. Explain that benefit may be backdated up to 3 months. Explain that he could appeal within 3 months, if he disagreed with the verdict

7. Explain what to do in practice

Explain that he should go to his local social security office and collect form B1 (100Pn). This covers occupational lung diseases. Say that you will write this down for him later.

8. Explore any outstanding concerns

Ensure that you have addressed all of his concerns.

9. Invite questions

Ask if he has any other questions.

10. Agree a way forward

Agree a clear course of action, ensuring that medical follow-up at clinic or with his general practitioner is in place.

Discussion

What types of asbestos lung disease make a patient eligible for compensation?

These are listed in Box 4.47.

Can compensation be considered for any other lung diseases?

Patients with a wide range of pneumoconioses, including coal worker's pneumoconiosis and silicosis, are eligible.

Can patients sue previous employers?

Yes, but many patients will have been exposed to asbestos from various workplaces and it may be difficult to prove that exposure in one workplace caused disease. Further, many employers no longer exist and legal expenses make legal action untenable.

Box 4.47 **Asbestos lung disease eligible for compensation**

- Mesothelioma
- Asbestosis
- Bilateral diffuse pleural thickening to a thickness of 5 mm or more at any point on chest X-ray
- Primary lung cancer with evidence of asbestosis or diffuse pleural thickening

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Integrated clinical assessment

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Skin problems

Examination of the skin

Introduction

Skin comprises an inner dermis of collagen and elastic tissue lying on subcutaneous fat, and an outer, continuously replenishing epidermis extending from a basal layer of cells with scattered melanocytes to a top layer of protective keratinocytes. These continuously degenerate and slough off to be replaced by cells from beneath. The epidermal–dermal junction is demarcated by a basement membrane. Skin disease can originate in any of these structures and skin, the only visible organ, can be a window to the world of systemic disease, for example: diabetes mellitus (necrobiosis lipoidica, infections); sarcoidosis (erythema nodosum, lupus pernio); inflammatory bowel disease (erythema nodosum); internal malignancy (dermatomyositis, paraneoplastic pemphigus); porphyria cutanea tarda, Graves' disease (pretibial myxoedema, thyroid acropachy, palmar erythema); Cushing's syndrome (thin skin, striae, bruising); Addison's disease (hyperpigmentation).

History

Important areas to cover are:

- Duration of symptoms, e.g. urticaria is rapid, psoriasis lesions are chronic
- Point of origin, e.g. extensors for psoriasis, flexors for atopic dermatitis
- Symptoms, e.g. dermatitis and scabies are itchy, herpes zoster is painful
- Provoking and relieving factors, e.g. sunlight relieves psoriasis but induces the rash of lupus and polymorphic light eruption
- Past medical history
- Medication history
- Social history, e.g. environment, travel, contacts
- Occupational history, e.g. contact dermatitis
- Family history, e.g. psoriasis and atopic dermatitis have a genetic basis.

Examination

In skin cases, be prepared to do two things:

- Look at the distribution of a rash (pattern recognition is important, e.g. photosensitivity)
- Describe lesions (the morphology may be diagnostic, e.g. psoriasis; if it not diagnostic, comment on differential diagnoses).

Distribution of skin lesions

You are likely to be asked to examine a particular region, e.g. the scalp, face, mouth, hands, nails or shins. If not, work from scalp to sole. Always attempt to describe the distribution of skin lesions, noting particularly if they are bilateral or symmetrical. As a rule, endogenous causes are more likely to produce bilateral lesions (e.g. psoriasis, see Fig. 5.1; Case 5.1) and exogenous causes produce a more random distribution.

Description of skin lesions

Central to dermatology is your ability to describe skin lesions (Table 5.1).

Summary

A summary of the skin examination sequence is given in the Summary box.

SUMMARY BOX – SKIN EXAMINATION SEQUENCE

- ◆ Look at the distribution of the rash, e.g. bilateral, symmetrical, photosensitive areas
- ◆ Be able to describe lesions (Table 5.1); the morphology may be diagnostic, e.g. psoriasis; if not diagnostic, comment on differential diagnoses
- ◆ Look for relevant non-cutaneous signs, e.g. psoriatic arthropathy.

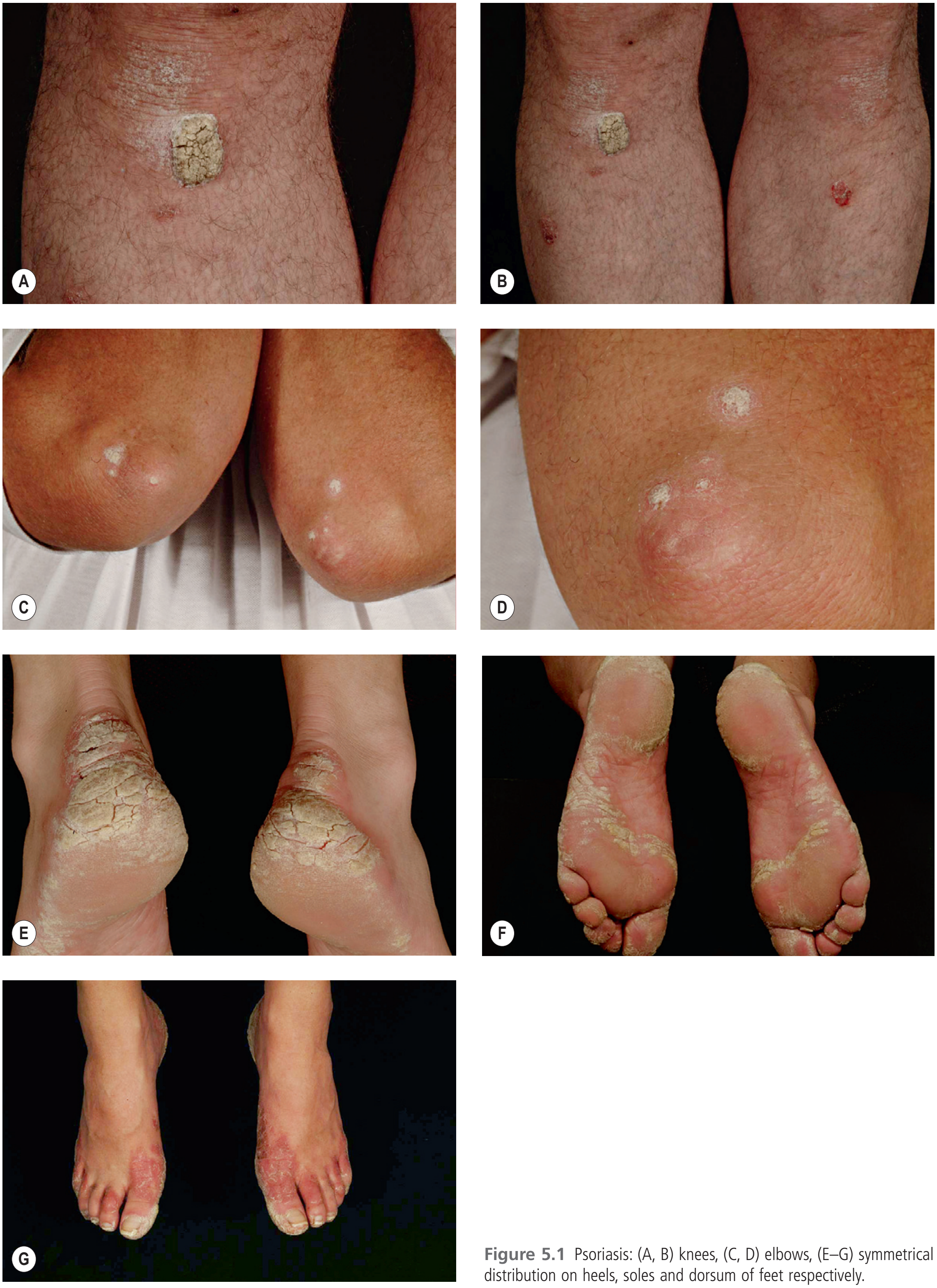


Figure 5.1 Psoriasis: (A, B) knees, (C, D) elbows, (E–G) symmetrical distribution on heels, soles and dorsum of feet respectively.

Table 5.1 Terminology for skin lesions

Term	Description
Macule	Flat area of discoloration ranging from pale (loss of melanin) to brown or black (increased melanin); many macules are red, indicating vascular dilatation or an inflammatory process
Patch	Large macule
Papule	Raised lesion > 1 cm in diameter
Nodule	Raised lesion < 1 cm in diameter
Plaque	Raised lesion with a flattened top, or plateau
Vesicle	Fluid-filled lesion or 'blister' < 0.5 cm in diameter
Bulla	Larger blister
Pustule	Vesicle filled with neutrophils (not necessarily infection)
Telangiectasia	Dilated, superficial blood vessels (capillaries, post-capillary venules) – idiopathic or associated with cold outdoor exposure, pulmonary hypertension, scleroderma, systemic lupus erythematosus, rosacea, lupus pernio or necrobiosis lipoidica diabeticorum
Discoid	Flat and disc-like lesion (term sometimes overlapping with nummular or coin-like lesions)
Annular	Ring shaped
Reticular	'Net-like' lesions, e.g. erythema ab igne (Granny's tartan) and livedo reticularis (physiological or associated with sepsis, connective tissue disease or malignancy)
Atrophy	Loss of tissue – loss of dermis or subcutaneous fat usually leaves a depression in the skin; loss of epidermis causes wrinkling and a translucent, hypopigmented appearance
Lichenification	Characteristic skin thickening (resembling lichen on rocks or trees) often produced by chronic inflammation or rubbing
Erosion	Area of lost epidermis that generally heals without scarring
Excoriation	Linear erosions often produced by scratching
Ulcer	Area of skin loss involving the dermis
Fissures	Slit through whole thickness of skin

Cases

CASE 5.1 PSORIASIS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mrs Jacquie Green, aged 33 years

This young woman is in the outpatient clinic for follow-up of recent lobar pneumonia and mentions that she has had a problematic rash for months on her knees and elbows.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 33-year-old woman in the outpatient clinic for follow-up of recent pneumonia. You have had a recurring rash, predominantly on your knees, elbows and hands but also around your scalp, for some years, but worse in the last few months since being unwell with asthma. It does not cause you particular problems but it is scaly, and worse in times of stress and relieved by sunlight. It also seems to flare up whenever you stop courses of steroid for asthma. It is rather irritating and you would be happy if there were some treatment available. You tried some coal tar treatment once and it was incredibly messy.

Focused history and examination

Initial history

- Ask about duration of symptoms. Psoriasis is a chronic condition that waxes and wanes.
- Ask about precipitating and relieving factors. Psoriasis is often worse in stress and flares up after stopping steroids, and improves with relaxation and sunlight.
- Ask about the distribution. Chronic plaque psoriasis is usually symmetrical, affecting extensor surfaces.
- Ask about the lesions themselves.

Initial examination

- Be aware of the commonest type of psoriasis – chronic plaque psoriasis, and of psoriasis variants (Table 5.2). Looks at the skin lesions and at the hands and nails.

Chronic plaque psoriasis

There are numerous symmetrically distributed plaques (Fig. 5.1) most prominent on *extensor surfaces (elbows, knees)*, the *scalp* and *hairline* and behind the *ears*, the *lower back (sacrum)*, the *shin* and the *umbilicus*. Plaques may range in size from a few millimetres to a large area of the limbs or trunk. These are *sharply marginated* and *pink/red*

Table 5.2 Psoriasis variants

Variant	Features	Differential diagnosis
Guttate psoriasis	Acute eruption of small plaques typically < 1 cm in diameter over trunk and limbs; these look like drops of rain or paint Common in adolescence Usually triggered by upper respiratory infection, e.g. streptococcal pharyngitis	Pityriasis versicolor Pityriasis rosea
Palmoplantar pustular psoriasis	Often chronic relapsing and remitting More common in females Scattered crops of pustules resembling ‘raindrops’ turn from white to ‘autumn-brown’ colour then fade Severe erythema, scaling and soreness Not generally associated with other forms of psoriasis	Pompholyx Dermatophyte infection
Generalised pustular psoriasis	Life-threatening acute eruption with systemic illness without past psoriatic history Sheets of pustules may merge to form lakes of pus over an erythematous and oedematous base Commonly affects flexures but spreads widely Usually no psoriasis history Sometimes associated with corticosteroid withdrawal	Acute exanthematous toxic pustuloderma
Flexural psoriasis	More erythematous than scaly May be exudative Axillae, groins, umbilicus and genitalia	Candida Seborrhoeic dermatitis Allergic contact dermatitis
Erythrodermic psoriasis	Exfoliative dermatitis with severe erythema and scaling over entire body Usually pre-existing psoriasis that is difficult to control	Drug eruption Eczema Icthyoses Cutaneous lymphoma
Nail involvement psoriasis	Pitting Onycholysis Dystrophy Subungual hyperkeratosis Features reflect psoriasis in the nail matrix and bed Often pink or yellowish area beneath nail, adjacent to free margin or an area of onycholysis (oil-drop sign)	Dermatitis (pitting) Alopecia areata (pitting) Drug or phototoxic reaction during psoralen ultraviolet A therapy (onycholysis) Dermatophyte infection (subungual hyperkeratosis)
Facial psoriasis	Uncommon but frontal hairline may be affected Sebopsoriasis, a variety of the Köbner phenomenon, may occur in seborrhoeic dermatitis	Seborrhoeic dermatitis Contact dermatitis Atopic dermatitis

with *silvery-white scaling surfaces* (sometimes said to resemble limpets).

Seventy-five per cent of people with psoriasis have onset before 40 years; 80–90% of people with psoriasis have chronic plaque psoriasis. The predominance of erythema or scaling can vary from patient to patient. Scratching of scales may result in a *waxy* appearance, although lesions are not usually itchy. Lifting larger scales (do not do this) may result in capillary bleeding (*Auspitz sign*). Occasionally, instead of scaling, the surfaces of plaques are covered by hard, thickened firmly adherent keratin. *Köbner's phenomenon*, in which lesions often appear at sites of minor trauma (e.g. surgical wound, trivial scratch, abrasion, burn), is a helpful diagnostic feature, and sometimes the first sign of psoriasis. Other causes of Köbner's phenomenon include lichen planus, pemphigoid and certain viruses, but it does not occur in dermatitis.

Hands and nails

There may be *nail pitting* and *onycholysis* and *arthropathy* of the hands.

Further assessment

- Ask about joint symptoms. Psoriatic arthropathy affects up to 10% of patients with psoriasis and may precede or follow skin disease by months or even years. There are, in theory, five types, although overlap is common (Table 5.3). If there is arthropathy, consider the tendency for HLA B27 spondyloarthropathies to overlap, common features being sacroiliac discomfort and enthesopathies such as plantar fasciitis.
- Explore concerns.

Table 5.3 Psoriatic arthropathy

Type	Features
Asymmetrical distal interphalangeal joint arthropathy	Relatively uncommon but the form most strongly associated with psoriasis; affected digits often show nail changes such as pitting
Rheumatoid-like hands	The commonest type; seronegative
Asymmetrical large-joint mono- or oligoarthropathy	Large joint pain or swelling
Spondyloarthropathy and sacroiliitis	Low back pain
Arthritis mutilans	Very uncommon, severely destructive type

Feedback to patient

This looks like psoriasis, a very common skin condition that tends to be scaly and patchy like this. It tends to wax and wane, although some people do find that it improves with sunlight and worsens with stress or if they have been unwell. I think that your general practitioner could provide some simple creams to help settle it down in the first instance. Coal tar can be effective but many people these days opt for newer creams for exactly the reasons you mention. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This lady has numerous symmetrically distributed plaques, most prominent on extensor surfaces (elbows, knees), the scalp and hairline. These are sharply margined and pink/red with silvery white scaling surfaces.

Provide a diagnosis or differential diagnosis with supporting evidence

These are features of chronic plaque psoriasis.

Outline an investigation and management plan

Most psoriasis is mild and responds to topical therapy – emollients, coal tar and pastes, dithranol or vitamin D3 analogues are all suitable first-line therapies for limited chronic plaque psoriasis. About 10–20% of patients have moderate–severe psoriasis as determined by the Psoriasis Activity Severity Index scoring > 10. Most of these will require second-line (phototherapy or systemic) therapy, and around 20% have arthritis. Cognitive behavioural therapy is effective in psoriasis triggered by psychological stress. If these standard therapies [Table 5.4] prove unsuccessful, other immunomodulatory or biological therapies are available [Table 5.5 and Fig. 5.2].

Table 5.4 Standard therapies in psoriasis

Treatment	Comment
Topical therapy	
Emollients	
Short-contact dithranol	Useful in incremental concentrations as first-line treatment for stable plaques, resulting in prolonged remission; stains plaques and hair and must not be applied for longer than directed, usually 30 minutes
Coal tar ointments and pastes	Easier to apply in hospital; messy but safe and effective for stable plaques but salicylic acid may also be needed to dissolve thick keratin
Vitamin D3 analogues/deltanoids, e.g. calcipotriol, tacalcitol	Useful for mild to moderate stable plaques; remission duration short so treatment is constant; high doses (extensive psoriasis) may cause hypercalcaemia
Other	Corticosteroids are effective but tachyphylaxis (rebound on withdrawal) is a major drawback; retinoids may have some benefit but are teratogenic; topical calcineurin inhibitors (tacrolimus, pimecrolimus) are effective on thin plaques only (face and flexures) but should not be combined with phototherapy
Phototherapy	
Ultraviolet B	Useful in widespread plaque or guttate psoriasis
Oral (or topical psoralens), followed by irradiation with long-wave ultraviolet A (PUVA)	Useful in widespread plaque psoriasis
Systemic therapy	
Ciclosporin	Rapid acting and highly effective; inhibits calcineurin; side effects are immunosuppression, hypertension and nephrotoxicity
Methotrexate	Widely used in extensive plaque psoriasis, generalised pustular psoriasis, erythrodermic psoriasis and psoriatic arthropathy; side effects are bone marrow suppression and hepatotoxicity
Acitretin	A treatment of choice for psoriasis as monotherapy or in combination with PUVA; teratogenic
Hydroxycarbamide	Less commonly used; causes bone marrow suppression

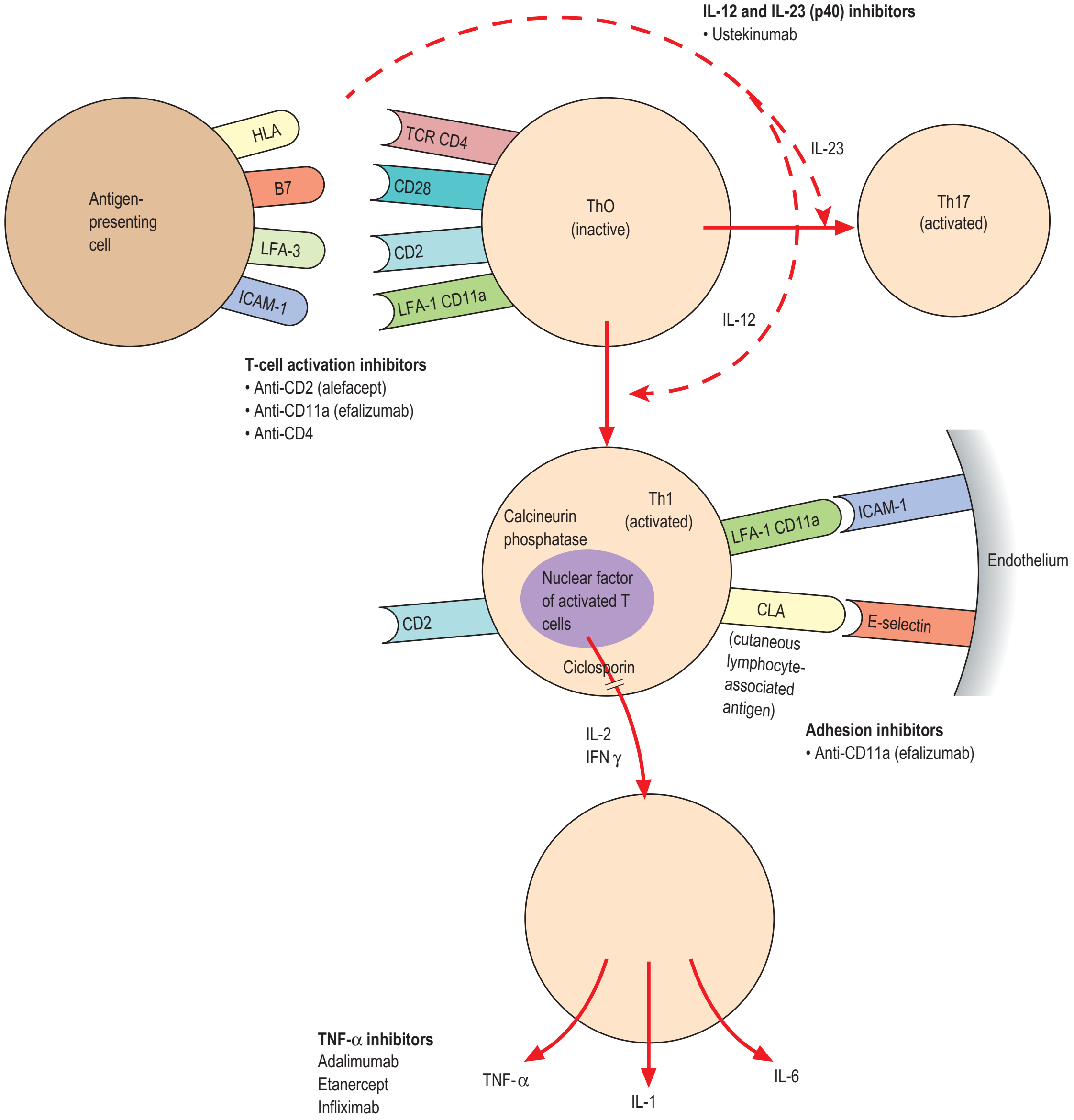

IL-12 and IL-23 (p40) inhibitors
• Ustekinumab
Antigen-presenting cell
HLA
B7
LFA-3
ICAM-1
TCR CD4
CD28
CD2
LFA-1 CD11a
ThO (inactive)
IL-23
Th17 (activated)
IL-12
T-cell activation inhibitors
• Anti-CD2 (alefacept)
• Anti-CD11a (efalizumab)
• Anti-CD4
Calcineurin phosphatase
Th1 (activated)
Nuclear factor of activated T cells
CD2
Ciclosporin
LFA-1 CD11a
ICAM-1
Endothelium
CLA
(cutaneous lymphocyte-associated antigen)
E-selectin
IL-2
IFN γ
Adhesion inhibitors
• Anti-CD11a (efalizumab)
TNF-α inhibitors
Adalimumab
Etanercept
Infliximab
TNF-α
IL-1
IL-6

Figure 5.2 Current and proposed immunomodulatory therapies or 'biologicals' in psoriasis. HLA, human leucocyte antigen; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; Th, T-helper; TNF, tumour necrosis factor.

Table 5.5 Other immunomodulatory or biological therapies in psoriasis

Biological	**How it works**
TNF-α inhibitors	Adalimumab
	Etanercept
	Infliximab

Table 5.5 Other immunomodulatory or biological therapies in psoriasis—cont'd

Biological		How it works
T-cell activation inhibitors	Alefacept	Binds T-cell receptor CD2 and inhibits T-cell activation that follows binding to LFA-3 on antigen-presenting cells
	Efalizumab	Humanised IgG1 monoclonal antibody against CD11a subunit of LFA-1, blocking LFA-1 binding to ICAM-1 and inhibiting both T-cell activation and adhesion of circulating T cells to ICAM-1-expressing endothelial cells and keratinocytes, thus preventing adhesion and migration of T cells
IL-12 and IL-23 inhibitors	Ustekinumab	Prevents binding of IL-12 or 1L-23 via p40

Immune rationale in psoriasis

There are two peaks of incidence of onset – before 40 years and 55–60 years, the former more likely to have a family history (associated strongly with HLA Cw6). Psoriasis probably arises from interaction of genetic susceptibility and physical (e.g. trauma, pregnancy, infection, drugs – lithium and beta blockers, steroid withdrawal) or psychological stress, producing innate immune responses and adaptive, acquired immune responses via T cells.

Up to 50% of psoriasis has a recognised genetic susceptibility, notable genes including *PSOR1* and *PSOR2*, interleukin (IL-12 and IL-23) genes, late cornfield envelope (LCE) genes (sharing with atopic dermatitis mutations in the filaggrin gene leading to disturbances in corneal barrier function which relies on the filaggrin protein) and the *PTPN22* gene disturbed in many autoimmune disorders including type 1 diabetes mellitus, rheumatoid arthritis and lupus.

Psoriasis is a predominantly T-helper type 1 (Th1) cytokine-mediated pro-inflammatory disease. IL-12 promotes deviation to Th1 lymphocyte production, and Th1-lymphocyte-derived cytokines IL-2 and interferon-γ (IFN-γ) are abundant in plaques. IL-2 and IFN-γ stimulate release of tumour necrosis factor-α (TNF- α), IL-1 and IL-6, key pro-inflammatory cytokines released from macrophages as final common mediators in the Th1-driven pro-inflammatory pathway. More recently recognised is the role of IL-23, which promotes a newly discovered T-helper-17 (Th17) pathway. IL-23 stimulates epidermal hyperplasia via TNF and IL-R20R2 mechanisms, and subunits of IL-23 (e.g. p40) are found in psoriasis skin lesions.

Leucocyte function-associated antigen 1 (LFA-1), a member of the integrin family of chemokines, is expressed on the surface of leucocytes; it comprises integrin subunits including CD11a (α) and aids leucocyte (including T-cell) activation and extravasation from blood to tissues. In pustular psoriasis, migration of neutrophils into the epidermis is especially pronounced, causing multiple, small, sterile pus deposits. CD11a binds intercellular adhesion molecules (e.g. ICAM-1) on endothelial cells, other leucocytes, fibroblasts and keratinocytes. Expression of ICAM-1 is induced by numerous cytokines, including TNF-α, IL-1 and IL-6.

The pro-inflammatory response in psoriasis leads to epidermal keratinocyte proliferation and thickening of the epidermis with thick keratin. However, rapid turnover prevents adequate differentiation into normal keratin and the keratin produced is scaly and readily removed. An equivalent process in the nail leads to thickening, pitting and onycholysis. Angiogenesis is also prominent, and when scales are removed a red vascular layer with capillaries reaching upwards is characteristic (*Auspitz sign*).

CASE 5.2 DERMATITIS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Ms Eleanor Whiting, aged 35 years

This young woman was admitted to your ward yesterday with asthma. She has a chronic skin rash that has worsened.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old woman admitted to hospital yesterday with worsening asthma. You mention to the admitting doctor that you have had a chronic itchy skin condition on the flexor surface of your arms and legs for many years but that it is worse. You are also concerned that the skin is breaking down much more easily than it used to, especially on the hands, where water and soap and possibly chemicals (you are a hairdresser) and the hot atmosphere appears to be preventing it from ever fully healing. You cannot give up work. You take occasional over-the-counter emollients.

Focused history and examination

Initial history

- Ask about the duration of symptoms.
- Ask about itch.

- Ask about atopic symptoms, e.g. asthma and hayfever.
- Ask about any provoking and relieving factors, notably any occupational or household allergens or irritants.
- Ask whether there is a family history.
- Ask about treatments to date.

Initial examination

- Note the distribution of the rash and its appearances. The *skin is red, swollen and blistering* or *dry, thickened and leathery, with erythema, scaling and evidence of scratching*. Both extremes are *itchy*.

Dermatitis and eczema are interchangeable terms. The term 'eczema' means skin 'boiling over'. There are many types of dermatitis and the clinical appearance can fall anywhere between the two extremes. Pathologically, there is breakdown in the skin's horny barrier and there may be oedema high in the dermis. Any blisters tend to have a honeycomb, multiloculated core, not typical of other blistering diseases such as pemphigus.

Further assessment

- Features of the history that should be further explored are atopy, occupation and exposure to irritants.
- Explore concerns.

Dermatitis may have endogenous or exogenous causes, the latter generally contact dermatitis and photosensitivity (Table 5.6). Bilateral dermatitis is more likely to have an endogenous cause and unilateral dermatitis an exogenous cause (but contact dermatitis commonly affects both hands if dipped in chemical irritants). It is worth remembering that the differential diagnoses of acute 'dermatitis' include infectious skin conditions such as scabies (intensely itchy and worse after hot showers or baths and at night; burrows of the scabies mite *Sarcoptes scabei* may be seen) and *Tinea pedis* in foot dermatitis, often unilateral, dry, scaly and interdigitate.

Dermatitis can be severe and even life threatening, especially with secondary infection. Apparent dermatitis occasionally represents a more sinister aetiology. An eruption resembling flexural atopic dermatitis is occasionally the result of agammaglobulinaemia, coeliac disease or mycosis fungoides.

Feedback to patient

This looks like eczema, also known as dermatitis, a very common condition that affects the areas in which you have it and gives rise to exactly this sort of dry and itchy skin. There are many causes or types. A common type, known as atopic dermatitis, occurs in people with hayfever or asthma. However, I suspect that you also have a type known as irritant contact dermatitis from the water and exposure to substances at work. I would be confident that some stronger creams or ointments could be used in the first instance to settle this down, and then we could ask your general practitioner to prescribe something a little less strong regularly to keep it settled down. I'd be happy to answer any further questions or concerns that you may have.

Table 5.6 Types of dermatitis

Type	Cause	Features
Atopic eczema	Th2-weighted allergic process Null mutations in the filaggrin (FLG) gene result in loss of epidermal protein filaggrin in the aetiology of atopic diseases. Filaggrin is needed for conversion of keratinocytes to the protein/lipid squames that form the stratum corneum, the outermost layer of the skin. Icthyosis vulgaris, a disease characterised by dry and scaly skin, was first recognised as a filaggrin mutation disease and an exceptionally strong filaggrin mutation association is now clear for atopic eczema Allergens include house dust mite important (its faeces contribute hugely to weight of old pillows!; it likes moist, sweaty atmospheres, preferring beds to curtains and carpets, but cannot survive in high, dry atmospheres above 3000 m), pollen, animal dander and pollution, interact with the genetic tendency Diagnosis aided by radioallergosorbent tests to identify allergen-specific IgE in serum; alternatively, skin prick testing introduces allergen into the skin, where it interacts with IgE bound to mast cells and causes histamine release and a consequent 'wheal and flare' (oedema and erythema) response	At least 50% of all dermatitis, prevalence increasing *Validated UK refined Hanifin and Rajka diagnostic criteria* *Itchy skin in last 12 months + ≥ 3 of:* *Onset before 2 years of age; typically develops in infancy, when a trial of milk and egg exclusion may be warranted; may wax and wane through adult life* *History of flexural involvement* *History of generally dry skin* *History of other atopic disease* *Visible flexural dermatitis; tends to affect flexors, with itch, erythematous macules, papules or papulovesicles that may become lichenified and excoriated* Superimposed staphylococcal or streptococcal infection, impeding response to steroids, common; herpes simplex type 1 may cause rapid worsening of dermatitis, especially atopic (eczema herpeticum/'Kaposi's varicelliform eruption')

Table 5.6 Types of dermatitis—cont'd

Type	Cause	Features
Irritant contact dermatitis (ICD)	Usually due to daily, regular exposure to trigger factor (thus more readily identifiable), e.g. hand dermatitis due to soaps, solvents or chronic skin wear and tear Thus early intervention crucial to successful treatment; the more chronic the process, the less likely to remit and if it does can rapidly reappear with re-exposure Atopic dermatitis predisposes to ICD	Often subclinical skin damage before skin begins to dry, crack and develop a smooth, shiny atrophic appearance Oedema and blistering may develop
Allergic contact dermatitis (ACD)	Type IV delayed hypersensitivity reaction to previously tolerated substance, e.g. nickel (clothing, including underwear, keys and money), cosmetics and fragrances (including 'hypoallergenic' cosmetics!), formaldehyde preservatives in shampoos, occupational chemicals (e.g. epoxy resins, chromate metal in cement and leather, rubber), nail varnish, colophony (glues, sticking plasters, pine trees) Patch testing screens for common triggers ICD may predispose to ACD, because disturbance of skin barrier function allows allergen penetration ICD and ACD exhibit identical inflammatory cell and cytokine profiles but memory T cells have no role in ICD	Unlike ICD, often sudden reaction to trace quantity of allergen (initial sensitisation occurs when the allergen penetrates the skin and binds to Langerhans antigen-presenting cells which provoke a T-cell sensitisation; subsequent elicitation occurs when the same allergen is encountered) May become widespread, spreading to areas of body not recently exposed
Photosensitive dermatitis	True sun-induced dermatitis rare. Much more common are other forms of dermatitis aggravated by sunlight and other photodermatoses such as polymorphic light eruption	Dermatitis in photosensitive distribution
Discoid / nummular dermatitis	Likely infection (staphylococcal superantigens)	Intensely itchy coin shaped lesions on limbs, often distributed symmetrically, affecting middle-aged to older adults
Venous dermatitis	Venous stasis	Swelling, sclerosis or atrophy on lower leg (often starting at medial malleolus) Haemosiderin deposition from extravasated blood causes brownish discoloration May develop ulceration
Seborrhoeic dermatitis (see Fig. 5.3)	Likely genetic predisposition, mediated by several factors, e.g. hormonal, dietary May be inflammatory response to *Pityrosporum ovale*, a yeast in human scalp	Erythematous plaques or patches on scalp, preauricular area, nasolabial folds, glabella or eyelids; may be otitis externa Despite the name, lesions dry, often with scaling surface, and not associated with excess sebum May be part of spectrum that includes dandruff Blepharitis (itchy lids and crusting lid margins with a dandruffy appearance and broken lashes) strongly associated with seborrhoeic dermatitis or staphylococcal infection; conjunctivae are glistening and swollen with excess lipid secretion and foaming of the lid margins
Pompholyx	Seasonal or without obvious trigger Contact dermatitis affecting palms sometimes also referred to as pompholyx	Intensely itchy blisters on palms
Juvenile plantar dermatosis	Not known but prevalence seems to be increasing *Tinea pedis* should be excluded by microscopy of skin scrapings	Shiny, glazed appearance to aspects of the soles of the feet in contact with footwear
Neurodermatitis	Trigger usually historical, the signs due to habitual rubbing and scratching	Chronic lichenified skin (lichen simplex chronicus)
Asteatotic dermatitis (eczema craquelé)	Not known	Dry, crazy-paving pattern of fissuring, especially on the limbs

IgE, immunoglobulin E; Th2, T helper type 2.

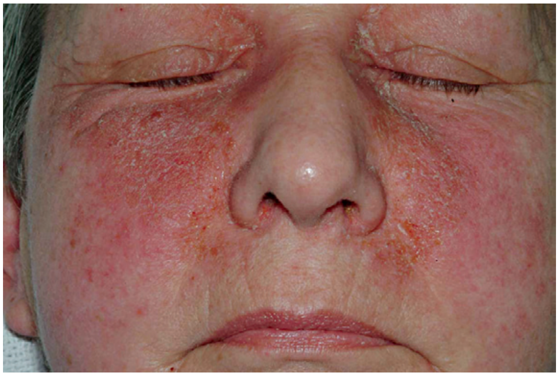


Figure 5.3 Seborrhoeic dermatitis.

Feedback to examiners

Summarise the key history and examination findings

This lady has red, swollen and blistering skin on her hands and dry, thickened, scaling skin on her arms.

Provide a diagnosis or differential diagnosis with supporting evidence

She probably has irritant contact dermatitis on a background of atopic dermatitis.

Outline an investigation and management plan

Chemical and allergen avoidance is the mainstay of prevention but not always practical. Patients should certainly avoid identified allergens (e.g. vacuuming, damp dusting) but improvement may take many months (e.g. after changing bedding). Emollients and emollient bathing promote skin hydration. Ointments and creams differ in their grease–water ratio. The epidermis can absorb both greasy and aqueous preparations. Generally, the greasy ointments are best for dry, scaling skin and watery creams for crusted weeping lesions. Pastes may be used for sustained action or occlusion. Topical corticosteroids (Box 5.1) are the main treatment for inflammation and pruritus. Less potent drugs should be used on the eyelids, face and flexural surfaces because of the risk of cataracts, skin atopy and telangiectasia. More potent treatment is allowable for these areas for a few days before stepping down to less potent maintenance treatment.

Topical/systemic antibiotics and antihistamines may be needed. Topical immunomodulators – tacrolimus and pimecrolimus – are very effective for intermittent use in mild to moderate atopic dermatitis, but should be applied thinly and only when needed to limit neoplastic risk. They do not cause skin atrophy and there is minimal absorption. They may be used on the face. Severe, refractory atopic dermatitis might need systemic corticosteroids; ciclosporin, azathioprine or mycophenolate mofetil are sometimes needed.

Box 5.1 **Potency of some typical corticosteroids**

Mild

- Hydrocortisone
- Fucidic acid and hydrocortisone (*Fucidin H*)

Moderate

- Clobetasone butyrate (*Eumovate*)

Potent

- Hydrocortisone butyrate (*Locoid*)
- Betamethasone valerate (*Betnovate*)
- Fucidic acid and betamethasone (*Fucibet*)
- Mometosone furoate (*Elocon*)

Very potent

- Clobetasol proprionate (*Dermovate*)
- Clobetasol proprionate, neomycin and nystatin (*Dermovate NN*)

CASE 5.3 LICHEN PLANUS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Graham Black, aged 33 years

This young man was admitted to your ward yesterday with asthma. He has a rash on his wrist.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 33-year-old man admitted to hospital yesterday with worsening asthma. You mention to the admitting doctor that you have had a very itchy rash on the flexor surface of your arms and legs. You have had it before but never this itchy.

Focused history and examination

Initial history

- Ask about the duration of symptoms and whether or not it has waxed and waned before.
- Ask about itch.
- Ask about any provoking and relieving factors.
- Ask about atopic symptoms, e.g. asthma and hayfever.
- Ask about treatments.

Initial examination

- There are *well-demarcated, polygonal, raised plaques on the flexor surfaces*, especially the *wrists* and *ankles* (Fig. 5.4). Their *flat tops* are *shiny* with a *violaceous colour*, interrupted by *milky white streaks – Wickham's striae*. They are very likely to be *intensely itchy*. There may be Köbner's phenomenon. Lesions usually resolve over a period of months to leave brownish macules.

Lichenification is a feature of many skin diseases such as eczema and itchy drug eruptions. The shiny, purplish flat tops of lichen planus, and their distribution, usually aid diagnosis.

Further assessment

- Look at the oral mucosa and nails. There may be white, 'net-like' lesions on the buccal mucosa (Fig. 5.5) or tongue (Fig. 5.6), often with ulceration. Atrophy and longitudinal grooves may affect the nail plates; sometimes nails disappear altogether.
- Explore any concerns.

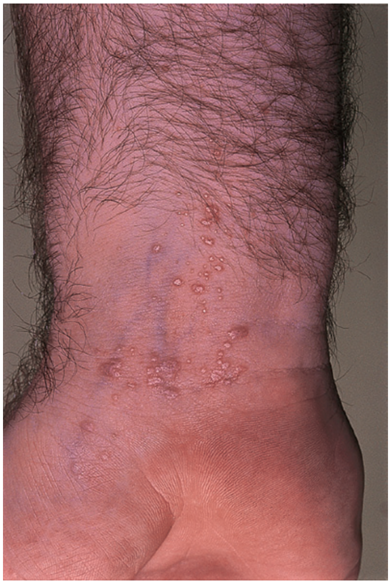


Figure 5.4 Lichen planus.

Feedback to patient

> I think this is probably a condition called lichen planus. It is usually quite harmless but very itchy and sometimes associated with eczema. It should all settle down very well with some mild steroid cream. I'd be happy to answer any questions you may have.

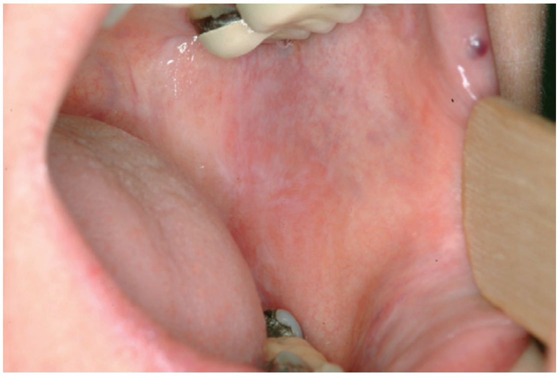


Figure 5.5 Lichen planus of buccal mucosa.

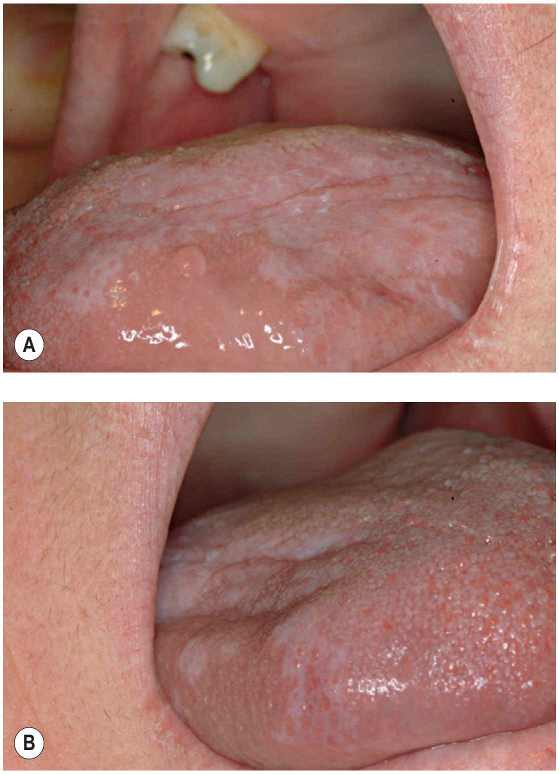


Figure 5.6 Lichen planus of tongue.

Feedback to examiners

Summarise the key history and examination findings

There are well-demarcated raised plaques on the flexor surfaces, especially the wrists. Their flat tops are shiny with a violaceous colour, interrupted by milky white streaks – Wickham's striae. They are very likely to be intensely itchy.

Provide a diagnosis or differential diagnosis with supporting evidence

Lichen planus is not life threatening, but white oral lesions may not be lichen planus; differential diagnoses include candidiasis and leucoplakia (hyperkeratotic lesions associated with Epstein–Barr virus), both more common in human immunodeficiency virus infection.

Outline an investigation and management plan

Lesions usually resolve over a period of months to leave brownish macules. The cause is uncertain, with no family history and no definite association with stress. The epidermis is thickened, with increased keratin (the white streaks imply a thickened granular layer and the basal layer is infiltrated with T lymphocytes in a band pattern). Moderately potent topical (occasionally systemic) steroids are effective for this condition, which appears to have an immune basis. Lichen planus is self-limiting but tends to relapse and remit over months or even years.

CASE 5.4 BLISTERING SKIN DISORDERS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Sydney Beech, aged 74 years

This man is on your ward for investigation of altered bowel habit. He mentions that he has a rather severe blistering rash that has developed in the past fortnight.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 74-year-old man in hospital for investigation of altered bowel habit. You mention to the doctor that you have a rather severe blistering rash on your thighs and trunk that has developed in the past fortnight, with tense, itchy lesions of varying sizes. You do not have any oral lesions. You are, however, keen to get home very soon as you wife has Alzheimer's disease, although family are looking after her.

Focused history and examination

Initial history

- Ask about the duration of symptoms.
- Ask about symptoms, e.g. pain, itch, weeping, crusting or bleeding.
- Ask about distribution.
- Ask about any provoking and relieving factors.
- Ask about treatments.

Initial examination

- Be aware of pemphigus and pemphigoid as important chronic widely distributed blistering diseases.

Bullous pemphigoid

There are *tense blisters* of *variable size* (much more variable than pemphigus, from a few millimetres to a few centimetres, but large, tense blisters up to 3 cm in diameter are typical) on the *flexor surfaces* spreading to the *trunk* (Fig. 5.7) on an erythematous base. Blisters may be broken because of excoriation. Early disease may appear as a pruritic, urticarial rash. Oral lesions are less frequent than in pemphigus, occurring in around one-third of patients and seldom a presenting feature. The anus, vagina and oesophagus are occasionally involved.

Pemphigus

There is a *bullous eruption* (in a middle-aged/older patient) comprising *flaccid, fragile, thin-walled blisters* on the *trunk* 1–2 cm in diameter (Fig. 5.8). Many have *burst*, leaving *red, exuding, tender patches* (even rubbing of normal skin can cause sloughing of the epidermis – Nikolsky's sign). *Oral erosions* (Fig. 5.9) are common and painful and may precede the rash. *Pemphigus foliaceous* is characterised by superficial blisters that affect only the skin. *Pemphigus vulgaris* is characterised by mucosal involvement and subsequent skin involvement with blisters and erosions.

Pemphigus is generally more serious than pemphigoid, although mucous membrane pemphigoid is a variant with predominant mucous membrane involvement, severe scarring and risk of blindness and laryngeal stenosis.

Further assessment

- Be aware of the list of differential diagnoses of blistering diseases (Table 5.7) and ask about any provoking or relieving factors.
- Explore concerns.

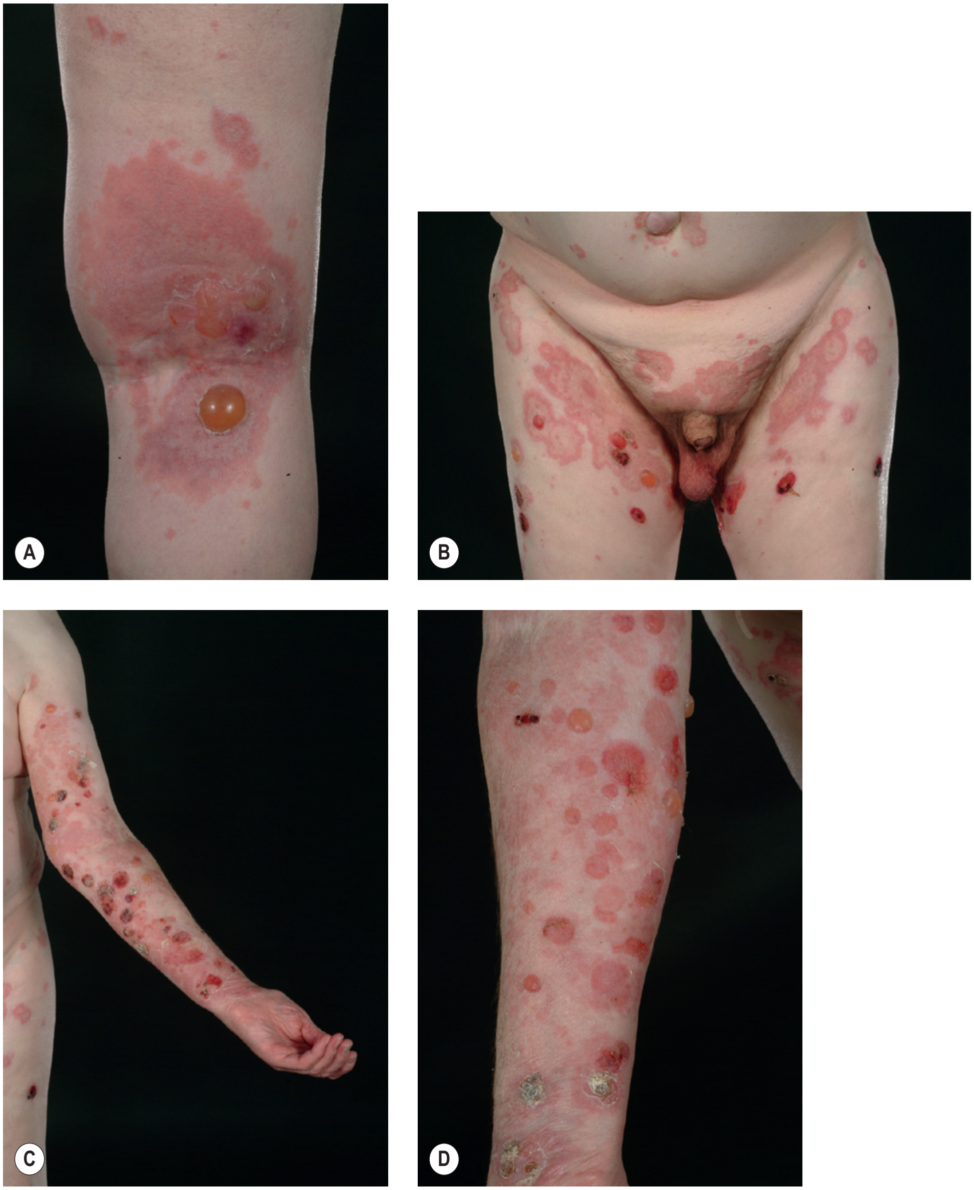


Figure 5.7 (A–D) Pemphigoid.

Feedback to patient

I think this is probably a condition called pemphigoid. This is probably not related to the bowel trouble, although there are some blistering disorders that can be related to bowel trouble. It can be a very uncomfortable condition as a result of the painful blisters and their breakdown, but fortunately it is very effectively treated. In the first instance I would be keen to seek the advice of a dermatologist who would confirm if this is pemphigoid and discuss the treatment options with you. I appreciate your need to get home soon. I'd hope that we can make a treatment plan for you very quickly, and ideally we'd keep you in hospital at least until we can be sure that the condition is stable and things are moving in the right direction. Shall we see what the dermatologist thinks first of all? I'd be happy to answer any further questions or concerns that you may have.

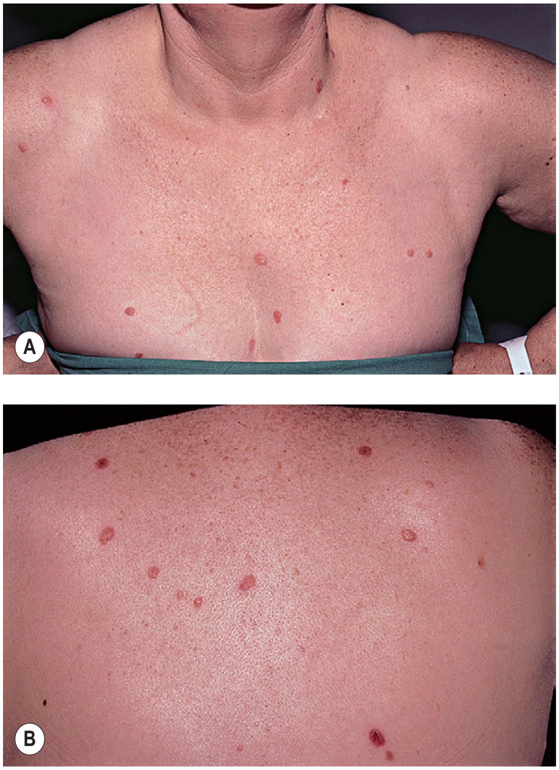


Figure 5.8 (A, B) Pemphigus – trunk.

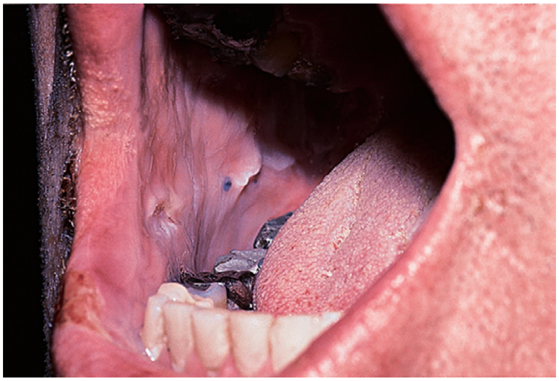


Figure 5.9 Pemphigus – intraoral.

Table 5.7 Important differential diagnoses of blistering diseases

Immunological	Pemphigoid
	Pemphigus
	Dermatitis herpetiformis – symmetrical, intensely itchy vesicles or urticarial plaques on trunk and extensor surfaces, buttocks and occasionally the face and scalp associated with gluten-sensitive enteropathy (coeliac disease) and granular deposition of IgA; responds to dapsone
	Lichen planus – white lacy pattern characteristic
Genetic	Epidermolysis bullosa (EB) – a group of hereditary disorders with blistering and erosions on minimal trauma, commonly with scarring and squamous cell carcinoma a late complication; EB simplex is a range of diseases with suprabasal splitting and blistering of limbs, healing without scarring; junctional EB is rare and often lethal; dystrophic EB is a range of diseases with subepidermal blisters below the dermo-epidermal junction
Inflammatory	Infection (staphylococcal – impetigo, streptococcal, herpes simplex, herpes zoster, coxsackie virus, fungal)
	Dermatitis
	Insect bites
	Erythema multiforme and Stevens–Johnson syndrome (severe bullous form) – crops of maculopapular erythema on limbs and trunk whose lesions may expand leaving a pale centre, the classic target lesion, and bullae / vesicles and / or necrosis may develop within targets and in mucous membranes; causes include herpes simplex, *Mycoplasma*, infectious mononucleosis, HIV, sulphonamides, penicillin, SLE, Wegener's granulomatosis, sarcoidosis
Physical	Heat and cold
	Irradiation
	Contact with irritants
	Friction / rubbing
	Oedema
Drug reactions	Fixed drug eruption
	Erythema multiforme
	Photosensitive eruption
	Toxic epidermal necrolysis
Systemic disease	Porphyria cutanea tarda
	Carcinoma

HIV, human immunodeficiency virus; IgA, immunoglobulin A; SLE, systemic lupus erythematosus.

Feedback to examiners

Summarise the key history and examination findings

This man has a blistering rash with tense variably sized blisters on his trunk and limbs of variable size and areas of excoriation.

Provide a diagnosis or differential diagnosis with supporting evidence

This is very likely to be pemphigoid. The blisters are of much more variable size and are tenser than in pemphigus [Table 5.8]. Oral lesions may occur in either condition. Other blistering conditions include infections, trauma, drug reactions and, rarely, cutaneous porphyria [Table 5.9].

Outline an investigation and management plan

I would ask a dermatologist to see this man. There are numerous differences between pemphigoid and pemphigus and it is very important to make an accurate diagnosis, not least because whilst both conditions may be treated with steroids there is a tendency to treat pemphigoid more sparingly whereas the approach to pemphigus, a more aggressive disease, should be more aggressive.

Table 5.8 Pemphigoid and pemphigus

	Pemphigoid	Pemphigus
Age of onset	Over 50 years	Wide range; peak 60–70 years
Pathophysiology	Autoimmune Splitting of cells at level of basement membrane Antibodies at dermo-epidermal junction in hemidesmosome (or a protein traversing the plasma membrane, linking to anchoring filaments and inserting to lamina densa)	Autoimmune, with antibodies against various elements of the desmosome Acantholysis – separation of epidermal keratinocytes from each other, i.e. splitting of cells within the epidermis – leading to blister formation Level of split subdivides types of pemphigus – just above basal layer in pemphigus vulgaris due to antibodies against desmoglein 3; superficial epidermal split in pemphigus foliaceous due to antibodies against desmoglein 1; other rare variations include pemphigus vegetans (a variant of pemphigus vulgaris with heaped up vegetating lesions in flexors), pemphigus erythematosus and paraneoplastic pemphigus
Clinical features	Described above	Described above
Complications	Most morbidity and mortality due to treatment – tendency now to treat less aggressively	Mucous membrane involvement may never fully resolve
Management	Oral then topical corticosteroids Occasionally azathioprine as steroid-sparing agent	Oral corticosteroids (higher dose than pemphigoid) Almost all patients require steroid-sparing potent immunomodulatory therapy, e.g. azathioprine, cyclophosphamide, mycophenolate mofetil, anti-B-cell therapy with anti-CD20 monoclonal antibodies such as rituximab
Prognosis	Often remits after 2–5 years	Mortality 15–25% (100% without treatment)

Table 5.9 Porphyrias*

Type	Enzyme block	Mode of inheritance	Clinical features	Diagnosis
Doss porphyria	ALA dehydratase (PBG synthase)	AR	Abdominal pain	↑ urinary ALA and copro III Normal faecal porphyrins
Acute intermittent porphyria	PBG deaminase (HMB synthase)	AD	Abdominal pain Tachycardia Hypertension or postural hypotension Constipation Motor peripheral neuropathy Muscle pain and weakness Chronic kidney disease Rhabdomyolysis Hyponatraemia Neuropsychiatric Most never develop symptoms	May be precipitated by drugs or infection Porphyrins that cannot be metabolised by the liver accumulate in the urine (even between attacks) turning it dark red on light exposure – ↑ urinary ALA and PBG
Congenital erythropoietic porphyria	Uroporphyrin III synthase	AR	Severe skin lesions with scarring Haemolysis	Normal ALA and PBG ↑ urinary and faecal porphyrins

Table 5.9 Porphyrias—cont'd

Type	Enzyme block	Mode of inheritance	Clinical features	Diagnosis
Porphyria cutanea tarda	Uroporphyrin decarboxylase (acquired inhibition of inhibitors forming in the presence of iron and oxidative environments, and so a significant proportion of people have haemochromatosis)	AD	Non-acute Marked skin lesions – blisters, erosions, pigmentation, scars and milia, especially of face, and secondary scarring Often secondary to chronic liver disease, especially alcohol or haemochromatosis or hepatitis C, or to oestrogens Increased risk of hepatocellular carcinoma	Normal ALA and PBG ↑ urinary and faecal porphyrins
Hereditary coproporphyria	Coproporphyrinogen oxidase	AD	Acute Skin vesicles Neuropsychiatric	↑ALA and PBG ↑ urinary and faecal copro III
Variegate porphyria	Protoporphyrinogen oxidase	AD	Acute Skin vesicles Neuropsychiatric	↑ faecal protoporphyrins
Erythropoietic protoporphyria	Ferrochelatase	AD	Photosensitivity	↑ red cell and faecal protoporphyrin IX

*Haem comprises a tetramer porphyrin ring with an iron molecule in its ferrous form. Porphyrias are enzyme disorders in the stepwise chain to haem synthesis (tabulation). These lead to loss of the production line ahead and accumulation of pre-haem metabolites (porphyrin precursors or porphyrins) behind the metabolic 'dam'. Accumulated metabolites early in the stepwise chain to haem synthesis tend to be water soluble, appearing in urine, and those later in the chain tend to appear in the stool. Important molecules early in the chain include aminolaevulinic acid (ALA) and porphobilinogen (PBG).

AD, autosomal dominant; AR, autosomal recessive.

The neuropsychiatric or acute porphyrias

Porphyrias causing neuropsychiatric manifestations include acute intermittent porphyria, hereditary coproporphyria and variegate porphyria. These are also known as the acute porphyrias or the hepatic porphyrias because they arise from enzyme abnormalities in the liver.

The cutaneous porphyrias

Skin disease is a feature of most porphyrias (acute intermittent porphyria a notable exception) because porphyrins become toxic when exposed to light. Photons of violet light electronically excite porphyrin molecules, which produce reactive oxygen species causing tissue damage directly and via other molecules such as metalloproteinases. Cutaneous porphyrias thus share common skin manifestations, including marked photosensitivity, blistering, erosions, pigmentation and scarring. Sunscreens are essential.

The acquired porphyrias

Most porphyrias are genetic, but porphyria cutanea tarda is often acquired; it is essentially a liver disorder presenting in the skin.

Diagnosis of porphyrias

Porphyrin precursors can be accurately analysed using high-performance liquid chromatography; assays of the enzymes are straightforward and molecular genetic studies are in widespread use.

Other conditions leading to porphyrin accumulation

Lead poisoning causes accumulation of porphyrins by inhibiting several steps in haem synthesis, which may lead to abdominal pain, motor neuropathy, a blue line on the gum and sideroblastic anaemia with basophilic stippling.

Treatment of acute porphyria

Avoiding precipitating factors is essential. Carbohydrate and intravenous haem therapy are synergistic in reversing the biochemical changes in acute attacks. Intravenous haem arginate inhibits ALA synthase, the initial and rate-limiting enzyme in the haem synthetic pathway. Liver transplantation is a potential treatment for those with recurrent, disabling attacks.

CASE 5.5 FACIAL RASH

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

> Re: Ms Harriet Tortoise, aged 45 years
>
> This woman is being investigated in your clinic for joint pains. She now has a facial rash.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 45-year-old woman being investigated in the general medical clinic for joint pains, the cause of which is not yet clear. Recently you developed a rash on your cheeks that appears to be made worse by sunlight. You have also noticed some pustules around the nose and are surprised to be developing what you believe to be acne. Your general practitioner prescribed some steroid cream, which seemed to make things worse.

Focused history and examination

Initial history

- Ask about any symptoms
- Ask about the duration of the rash.
- Ask whether there is a rash elsewhere.
- Ask about any provoking (e.g. sunlight) and relieving factors.
- Ask about treatments.

Initial examination

- Be aware of the most likely causes of a facial rash listed below.

Systemic lupus erythematosus (SLE)

There is a *'butterfly distribution' malar rash* (Fig. 5.10). There are *raised or flat patches of malar erythema, sparing the nasolabial folds*. Other areas such as the forehead and neck are often affected. There may be marked *photosensitivity*. There may be *mouth ulcers*.

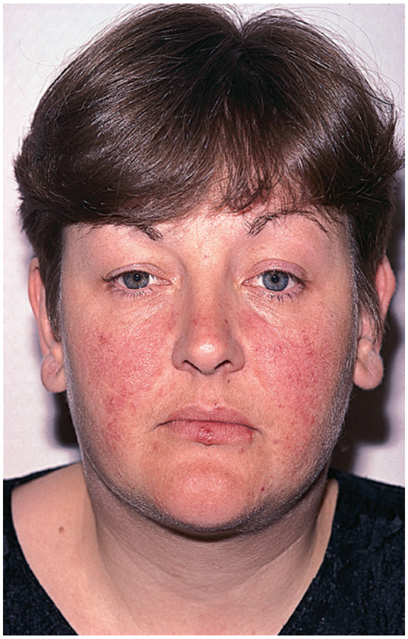


Figure 5.10 Malar rash.

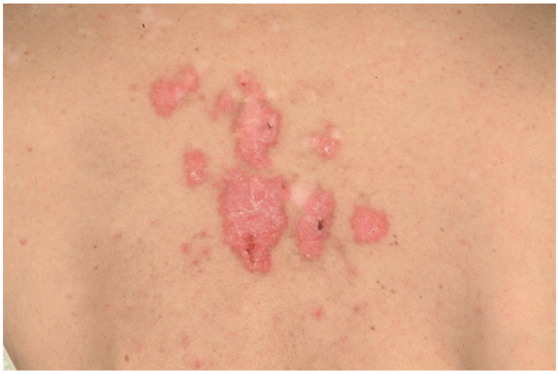


Figure 5.11 Discoid lupus erythematosus.

Discoid lupus erythematosus (DLE)

DLE is a skin-limited disease, with well-defined erythematous papules or plaques on light-exposed areas including the head, neck, hands and arms. Mostly affected are the cheeks, nose and forehead (Fig. 5.11). Like SLE, the rash is photosensitive, and more common in females. Lesions are scaling and hyperkeratosis of hair follicles gives these scales a dotted, 'nutmeg' appearance. If you were to remove the scales and inspect their undersurface, you would see spicules projecting from them. This is known as follicular keratosis or plugging (also known as the 'carpet track' sign) and no other scaling condition does this; it is specific to lupus. There may be patches of depigmentation. Once affected areas heal and the scab falls off, the skin beneath is often scarred, hypopigmented and atrophic.

Rosacea

There is an *erythematous, 'acneiform' papular eruption* on the *flush areas* or convexities of the face – *forehead, nose, cheeks,*

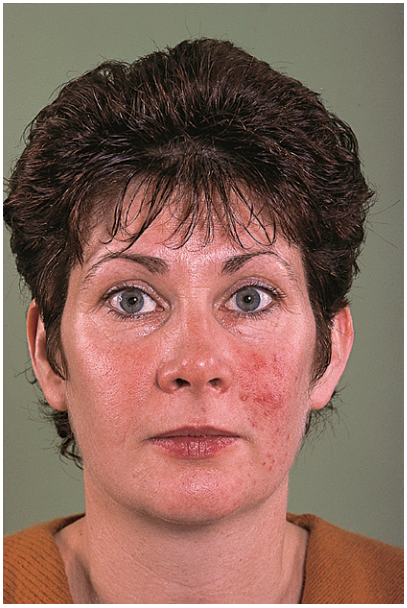


Figure 5.12 Rosacea.

chin (Fig. 5.12). The distribution is usually symmetrical; occasionally one side of the face is affected, and, rarely, other sites – the 'V' of the chest, upper arms and back.

There are two main clinical components to rosacea, vascular (episodic flushing, erythema and telangiectasia) and inflammatory (erythematous papules and pustules). *Pustules* within the eruption are almost pathognomonic. Later in disease, there is sebaceous hyperplasia, but seborrhoea and comedones (features of acne) are not features.

Seborrhoeic dermatitis

Seborrhoeic dermatitis is discussed in Case 5.2.

Dermatomyositis

There is a *heliotrope* (referring to the distinctive lilac colour of the flower so named) *rash* around the *eyelids* (Fig. 5.13). It may also affect the malar region, limb extensors, knuckles and trunk.

Gottron's papules may be present on the dorsum of the hands (notably metacarpophalangeal joints and interphalangeal joints) and occasionally elsewhere. *Nail-fold erythema* due to *dilated capillaries (telangiectasia)* is often present, and the cuticles may be ragged.

Lupus pernio

There are *purple/red/violaceous plaques on the nose, cheeks and earlobes* with *telangiectasia over and around the plaques* (Fig. 5.14). The plaques may have a yellowish translucency. They tend to flatten with time.

Lupus vulgaris

This is the skin manifestation of tuberculosis and is rare in the UK. The lesion has an 'apple jelly' consistency when a translucent slide is rested upon it.

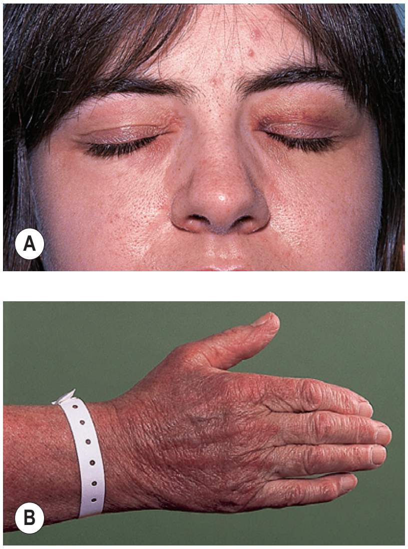


Figure 5.13 (A, B) Dermatomyositis.

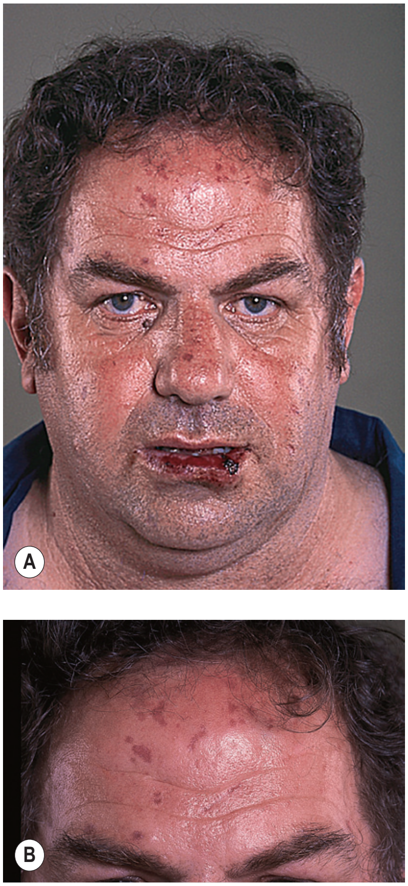


Figure 5.14 (A, B) Lupus pernio.

Pulmonary hypertension

This is another cause of a malar rash.

Xanthelasmata

There are multiple *xanthelasmata* (see Fig. 5.94, p. 870).

Other acute causes of facial erythema, unlikely in PACES, include erysipelas, acute flares of dermatitis, polymorphic light eruptions and phototoxic eruptions. And causes of swollen eyelids specifically include allergic contact dermatitis, nephrotic syndrome, hypothyroidism and superior vena cava obstruction.

Further assessment

- Be aware of some distinguishing features between the facial rashes and of some important associations and complications of the facial rashes (Table 5.10).
- Explore concerns.

Feedback to patient

> I think you may have a condition called lupus. This is a condition in which the body's immune system becomes overactive and antibodies, which would normally be used by the body to, for example, fight infection, instead attack areas of the skin. It is very common for people with lupus to have skin and joint problems caused by this phenomenon. It can be a very uncomfortable condition but happily there are usually very effective treatments. However, lupus does not cause a rash immediately adjacent to the nose whereas there is a condition called rosacea that can. In the first instance I would be keen to arrange some blood tests to try to help us and to ensure that other parts of the body are not affected. I would also like to ask a dermatologist (skin specialist) and rheumatologist (joint specialist) to see you to discuss the best forms of treatment. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

> This woman has a 'butterfly distribution' malar rash with patches of erythema, and may be describing photosensitivity. She also has nasolabial fold pustules

Table 5.10 Facial rashes – distinguishing features and associations

	Distinguishing features	Associations and complications
Systemic lupus erythematosus	Spares the nasolabial folds Pustules not a feature	Multi-organ involvement, e.g. joints, kidneys, lung, nervous system
Discoid lupus erythematosus	Spares the nasolabial folds Pustules not a feature Scaling, follicular plugging and scarring are features of lupus but not rosacea	Not associated with multi-organ involvement
Rosacea	May not spare the nasolabial folds Pustules characteristic Scaling unusual	Complications more common in males Rhinophyma (overgrowth of fibrous tissue and glands on nose, often seen in elderly men as thickened erythematous skin with enlarged follicles) Lymphoedema (particularly under eyes) Ocular involvement (blepharitis, conjunctivitis, episcleritis and keratitis) Pyoderma faciale (rosacea fulminans), originally thought an acne variant but may be a form of rosacea
Seborrhoeic dermatitis	Involves the scalp, nasolabial folds or eyelids Scaling characteristic However, seborrhoeic dermatitis and rosacea may coexist	Marginal keratitis
Dermatomyositis	Characteristic colour Not pustular	Polymyositis Occasionally associated with neoplasms, e.g. colorectal, ovarian, breast, lung
Lupus pernio	Not pustular Surface of nose thickened in lupus pernio, although telangiectactic, smooth and lacks the rugose peau d'orange surface of rhinophyma	Multi-organ involvement from sarcodiosis, e.g. lungs, central nervous system
Lupus vulgaris	Not pustular	Unrecognised or untreated tuberculosis
Pulmonary hypertension	Other signs, e.g. signs of mitral stenosis	Problems of underlying cause Cardiac decompensation
Xanthelasmata	Yellowish deposits around the eyes	Dyslipidaemia

Box 5.2 **Rosacea and acne vulgaris**

Rosacea

Rosacea is a common, chronic inflammatory skin disease tending to affect middle-aged patients (mostly 30–50 years), especially females. Precipitating factors include heat, sun, alcohol, spicy foods, emotion / embarrassment and corticosteroids. A *Demodex folliculorum* theory implicates pilosebaceous follicular mites as an underlying cause, but this is not certain.

Acne vulgaris

The aetiology and pathology of acne and rosacea are not related. Acne is a chronic inflammatory disorder of sebaceous glands associated with hair follicles, characterised by comedones (non-inflamed lesions), erythematous papules, pustules and nodules (inflamed lesions) and scarring. Scarring tends to be hypertrophic and keloid (trunk) or 'ice pick' (cheeks). Acneiform lesions are mostly on the face, back, chest and anogenital region, the distribution of pilosebaceous structures, although sebaceous glands are also distributed in areas not associated with hair follicles, including the eyelids (whose follicles are separate structures) and these do not give rise to acne. Sebaceous glands secrete triglycerides, fatty acids, wax and sterols as sebum. Four main factors conspire to cause acne:

1. There is primarily an increase in androgen-induced seborrhoea by sebaceous glands, although testosterone levels are not increased, and there is a correlation between sebum rate and acne severity.
2. Abnormal proliferation and differentiation of pilosebaceous ductal keratinocytes is central to increased sebum production and leads to formation of the primary acne lesion, the microcomedone (commonly present in normal-looking skin). Thickening or cornification of the keratin lining is associated with increased sebum lipid content and keratinocyte comedogenesis. Larger lesions are visible as comedones, comedones representing retention of hyperproliferating ductal corneocytes. Comedones may be open forming 'blackheads' (the colour mainly caused by melanin, not dirt) or closed forming 'whiteheads'.
3. Duct occlusion leads to enlargement of the sebaceous gland, leakage of sebum into the dermis and colonisation of the sebaceous gland and duct with *Proprionibacterium acnes* and other bacteria.
4. A significant inflammatory infiltrate is seen around follicles before evidence of comedone formation, but inflammation remains prominent as acne progresses as red papules, pustules and nodules.

Treatment involves tackling the above four factors.

- Seborrhoea may be treated by reducing either sebaceous gland size with isotretinoin or androgen drive with anti-androgens and oral contraceptives.
- Sebaceous gland blockage may be treated with retinoids or benzoyl peroxide.
- Bacterial colonisation is treated with antibiotics, benzoyl peroxide or azelaic acid.
- Inflammation is treated with retinoids, antibiotics and, in severe cases, oral or topical corticosteroids.

For mild acne, topical retinoid targets comedogenesis in combination with a topical antimicrobial such as benzoyl peroxide or erythromycin. Moderate acne may require oral antibiotics (or hormonal therapy) in addition to topical therapy. For severe acne oral isotretinoin may be indicated, a dietary metabolite of vitamin A with anti-inflammatory, regulatory and inhibitory effects on sebaceous glands, but it is teratogenic.

and an almost 'acneiform' eruption on the flush areas of the face.

Provide a diagnosis or differential diagnosis with supporting evidence

The 'butterfly' rash with photosensitivity and a history of joint pains would suggest lupus. However, the nasolabial folds are spared in lupus and the pustules here characteristic of rosacea [Box 5.2]. Adult onset 'acne' is not likely. Furthermore, whilst a lupus rash is helped by topical steroid, rosacea is often made worse, certainly on withdrawal.

Outline an investigation and management plan

I would value the opinion of a dermatologist. Treatments for the rash of lupus include moderately potent topical steroids and hydroxychloroquine. Sunscreens are essential. A subacute form of skin lupus may occur in an older person who is photosensitive but provoked by drugs such as thiazides, calcium channel blockers, antifungals and biologicals. However, for rosacea, corticosteroids should not be used. They are not effective in the long term and tend to cause skin addiction and 'flares' of severe rebound erythema, which do not easily settle. Avoidance of precipitating factors is seldom helpful except for the use of sunscreens. Topical treatments include metronidazole or erythromycin gel, with an emollient. Systemic treatments include tetracycline (often prolonged as low-dose maintenance treatment), minocycline and doxycycline. Although remissions with treatment occur, long-term treatment is usually needed. Topical tretinoin helps vascular features and, in severe cases, pulsed dye laser therapy is used.

CASE 5.6 SCLERODERMA, VITILIGO AND AUTOIMMUNE SKIN DISEASE

Candidate information

Role

You are a doctor on the cardiology ward.

Scenario

Re: Mrs Audrey Weatherborne, aged 79 years

This woman is on your ward recovering from a myocardial infarction. She mentions that she has had tightening of her fingers and facial skin for some years.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 79-year woman recovering in hospital from a heart attack. You seldom have cause to see a doctor but for some years have noticed that the skin over your hands, face and feet has become more tight and shiny, and you suffer considerably from cold hands and feet. You wonder what might be wrong. You are on a range of medications but have not been given beta blockers.

Focused history and examination

Initial history

- Ask about symptoms, e.g. pain, tightening skin, shiny skin, Raynaud's phenomenon (and clarify that she is not taking beta blockers).
- Ask about the duration of symptoms.

Initial examination

- Look at the face and hands.

Scleroderma – face

There is facial *telangiectasia*. The skin is *smooth, shiny* and *tight*. There is *perioral skin puckering* (Fig. 5.15).

Scleroderma – hands

There is *sclerodactyly, nail-fold erythema due to dilated nail-fold capillaries* (telangiectasia), *nail-fold infarction, ragged cuticles, digital ischaemia, pulp atrophy, calcinosis* and *Raynaud's phenomenon*.

Further assessment

- Distinguish limited from diffuse cutaneous systemic sclerosis. The latter extends above the elbows or knees or involves the trunk. You would confirm the diagnosis and stratify risk using hallmark antibodies and evidence of other organ disease.
- Ask about gastrointestinal symptoms (gastro-oesophageal reflux leading to Barrett's oesophagus) and kidney problems.

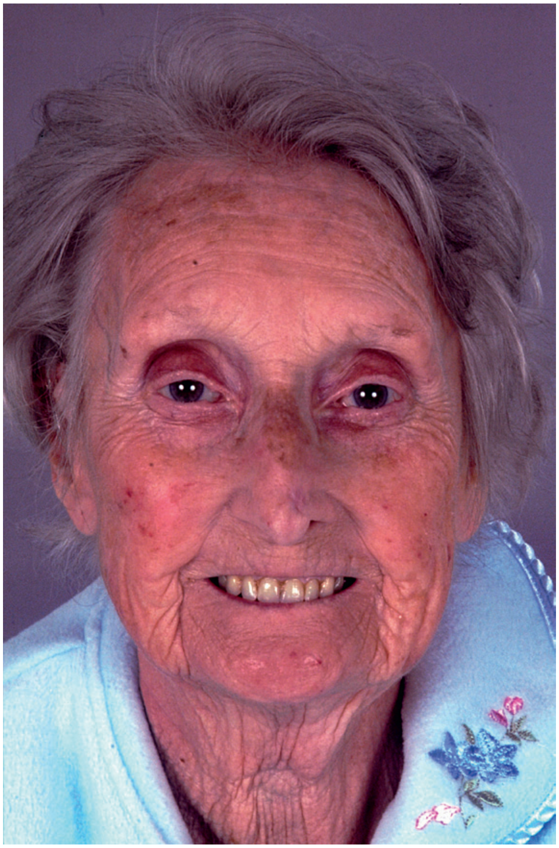


Figure 5.15 Scleroderma.

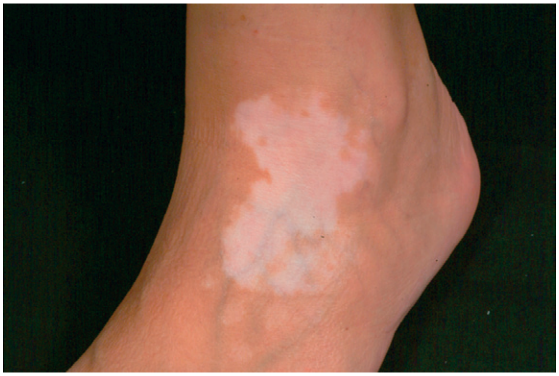


Figure 5.16 Vitiligo.

- Examine the chest for evidence of interstitial lung disease and signs of pulmonary hypertension.
- Skin signs are common in autoimmune connective tissue diseases (Box 5.3, Fig 5.16).
- Explore concerns.

Box 5.3 **Skin signs in autoimmune connective tissue diseases**

Raynaud's phenomenon

- Part of scleroderma spectrum
- Cold white hands (ischaemia), turn blue (stasis) then red (reactive hyperaemia) with pain

Rheumatoid arthritis

- Cutaneous / nail-fold vasculitis
- Nodules
- Pyoderma gangrenosus

Systemic lupus erythematosus

- Malar erythema, sparing nasolabial folds

Dermatomyositis

- Heliotrope rash (especially of eyelids)
- Gottron's papules
- Nail-fold erythema

Vitiligo

- Often idiopathic
- Often associated with autoimmune disease (see Fig. 5.16)

Alopecia areata

- Diffuse, patchy hair loss which does not scar (the hair follicles are not destroyed); 'exclamation mark' hairs may be seen 'sprouting in the desert' (other causes of non-scaring alopecia include male pattern baldness, stress, hypopituitarism, thyroid disease, hypoparathyroidism, diabetes mellitus, pregnancy and drugs, e.g. cytotoxics, antithyroid drugs, anticoagulants; scarring alopecia can occur in psoriasis, dermatitis, lichen planus, fungal / other infections, trauma / burns, lupus, morphoea and sarcoidosis)

Feedback to patient

I think you may have a condition called scleroderma. This is a skin condition that can cause all of the symptoms you have experienced, including a phenomenon called Raynaud's phenomenon in which the hands and feet can go very cold. There is a range of treatments but before starting anything it would be important to do three things. Firstly we should carry out some blood tests to try to establish the diagnosis with certainty. Secondly we should consider running some further tests to examine the possibility of the scleroderma affecting other regions of the body, which it sometimes can, including the lungs and the kidneys. Thirdly we should ask a rheumatologist to see you, as scleroderma is an area of his or her expertise. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has facial telangiectasia and perioral skin puckering. In her hands there is sclerodactyly and evidence of digital ischaemia, and she reports Raynaud's phenomenon.

Provide a diagnosis or differential diagnosis with supporting evidence

She has scleroderma. She may have limited or diffuse systemic sclerosis with multi-organ involvement, although the absence of apparent involvement above the elbows or knees would suggest limited systemic sclerosis.

Outline an investigation and management plan

I would arrange for her to have a range of blood tests including scleroderma hallmark antibodies and, depending upon symptoms, pulmonary function tests for interstitial lung disease, echocardiography for pulmonary artery hypertension, oesophagogastroduodenoscopy for Barrett's oesophagus and monitoring of renal function.

CASE 5.7 ORAL LESIONS AND NAIL LESIONS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Georgina Tate, aged 73 years

This woman is on your ward with iron deficiency anaemia. She has a skin rash around her mouth and hands.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 73-year-old woman in hospital with iron deficiency anaemia, and have been transfused with blood. You

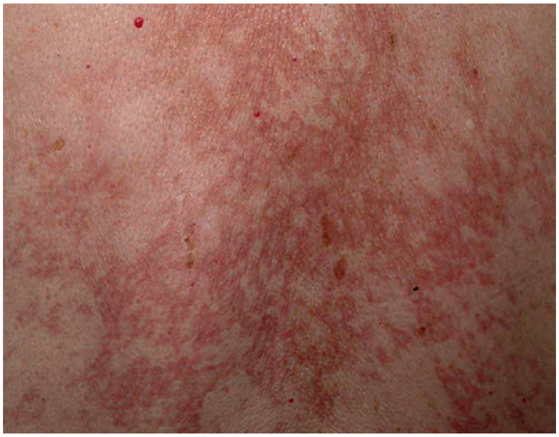


Figure 5.17 Telangiectasia.

have a chronic skin rash around your mouth and on your hands that waxes and wanes. You have a long history of iron deficiency anaemia and have been investigated and given a name for this before, although you cannot remember the name of the condition. You also have odd spoon-shaped nails. You would like to know a little more about the underlying condition.

Focused history and examination

Initial history

- Ask about the rash.
- Ask about a longstanding history of iron deficiency anaemia.
- Ask if there is a family history of similar rashes or anaemia.

Initial examination

- Be aware of common oral lesions seen in PACES, listed below.

Hereditary haemorrhagic telangiectasia (HHT)

There are *dilated capillaries / venules of the lips and tongue* and *around the mouth* (Fig. 5.17), *nail beds, hands* and frequently elsewhere. There may be evidence of recent epistaxis.

Peutz–Jeghers syndrome

The *lips* are *pigmented* in this autosomal dominant disorder characterised by mucocutaneous melanosis (lentigo) and gastrointestinal hamartomas.

Mouth ulcers and intraoral lesions

Causes are listed in Box 5.4.

Box 5.4 **Causes of mouth ulcers and intraoral lesions**

- Aphthous ulcers
- Traumatic ulcers
- Lichen planus
- Infection, e.g. candidiasis, herpes simplex virus
- Stevens–Johnson syndrome
- Pemphigus
- Carcinoma
- Behçet's disease
- Crohn's disease

Other

Other oral lesions you could encounter include perioral dermatitis and Addison's disease pigmentation. The circumoral and mucosal pigmentation of Peutz–Jeghers syndrome is usually less diffuse than that of Addison's disease.

Further assessment

- Nail lesions are seldom isolated in PACES, but be aware of the range of nail lesions that occur (Table 5.11). This woman probably has koilonychia associated with her iron deficiency anaemia and pallor from gastrointestinal haemorrhage.
- In HHT there may be arteriovenous malformations – direct connections between arteries and veins – throughout the gastrointestinal tract, liver, lungs and nervous system. Consider the possible presence of hepatic or chest bruits. Neurological problems in HHT may result from an intracranial arteriovenous malformation (subarachnoid haemorrhage is one of the most serious complications of HHT) or from an embolic stroke arising from a pulmonary arteriovenous malformation.
- Explore concerns.

Feedback to patient

> This looks like a condition called hereditary haemorrhagic telangiectasia, in which small blood vessels can be friable and leak small amounts of blood, giving rise to blood loss and a deficiency of iron. Interestingly, this can also give rise to the shape of your nails. It may be inherited. There is no specific treatment other than maintaining blood levels as far as possible with iron supplementation and blood transfusion if necessary. Further investigation is probably not necessary if this is a diagnosis that has been established previously and if there are no other conditions or complications in your past that might relate to this condition. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

> This lady has telangiectasias of the lips and tongue and around the mouth and hands together with koilonychias and she would thus appear to be iron deficient.

Table 5.11 Nail lesions

Lesion	Distinguishing features of nail lesions	Other systems in nail lesions
Psoriasis – causes keratin thickening of the nail.* Loss of minute plugs of normal keratin results in characteristic *pitting* and sometimes the thickened, dystrophic nail separates from its nail bed (*onycholysis*)	Pitting characteristic but not pathognomonic Onycholysis (often with discoloured, thickened, hyperkeratotic but brittle, dystrophic nails) may also be caused by fungal infection (onychomycosis, see Fig. 5.18), trauma, dermatitis, peripheral vascular disease, thyrotoxicosis (Plummer's nails) or be idiopathic, sometimes associated with excessive wetting of nails and chronic bacterial paronychia	Psoriatic arthropathy
Clubbing	Clubbing progresses through four phases: 1. Swelling of the soft tissues of the terminal phalanx with fluctuant nail beds 2. A permanently decreased angle between the nail plate and the posterior nail fold (this defines clubbing) 3. Increased curvature of the nails due to soft-tissue hypertrophy 4. Hypertrophic pulmonary osteoarthropathy, a rare and most extreme form. *Shamroth's sign* may be used to confirm 2 and 3 – when the distal phalanges of corresponding digits of opposite hands are directly apposed, fingernail to fingernail, a small diamond-shaped window is apparent between the nail beds; if obliterated, the test is positive and clubbing is present	May be caused by chronic suppurative lung disease, lung cancer, idiopathic pulmonary fibrosis, infective endocarditis, congenital cyanotic heart disease, chronic liver disease and inflammatory bowel disease; it may be congenital or idiopathic
Lichen planus	No pathognomonic features but occasionally causes atrophy of the nail plate (which may disappear altogether or exhibit longitudinal furrows) and the cuticle may advance forwards	Intraoral lesions
Nail lines	*Beau's lines* are *transverse* depressions representing altered growth rate and are a non-specific sign of previous illness or physiological change. *Onychomedesis* refers to shedding of the nail, which may occur in severe illness. *Longitudinal* depressions or ridges may occur in lichen planus, alopecia areata and Darier's disease	History of systemic illness with Beau's lines
Leuconychia	The nails appear white (a little subjective)	Chronic liver disease
Koilonychia	The nails (especially fingernails) are brittle and concave or 'spoon shaped'	Causes of iron deficiency
Onychogryphosis	Hypertrophy of the nail plate, often from chronic trauma	
Discoloration	Yellow/brownish tinge – dystrophic nails of any cause 'Half and half nails' in which proximal halves are pale and the distal halves pink – chronic kidney disease Isolated pigment beneath a nail – subungual melanoma Blue tinged lunula – Wilson's disease Yellow, curved nails – yellow nail syndrome Drug staining – tetracyclines (yellow), antimalarials (blue)	

*Nails comprise a nail bed, on top of which grows the highly keratinised nail plate (between the posterior and lateral nail folds and anterior free margin) from the nail matrix beneath the lunula and cuticle.

Provide a diagnosis or differential diagnosis with supporting evidence

The diagnosis is likely to be hereditary haemorrhagic telangiectasia. This is usually unmistakable when overt, but mild forms with expression in later life occur, for example with iron deficiency anaemia.

Outline an investigation and management plan

Hereditary haemorrhagic telangiectasia refers to a group of autosomal dominant diseases genetically linked to chromosomes 9 and 12. In some families the implicated gene encodes endoglin, a protein on

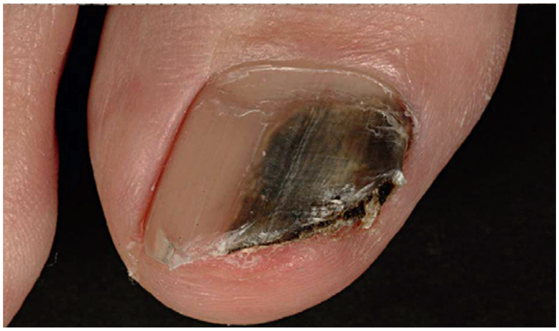


Figure 5.18 Onychomycosis.

endothelial cells that binds transforming growth factor-β. Management is aimed at maintaining satisfactory haemoglobin levels and being vigilant for complications, notably bleeding from arteriovenous malformations in other organs such as brain.

CASE 5.8 SHIN LESIONS

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Ms Jane Tiller, aged 22 years

This woman has presented to the acute medical unit with some lesions on her legs.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a previously well 22-year-old woman who has recently been given antibiotics by her general practitioner for a sore throat. You have now been admitted to the acute medical unit because of some very tender, bruise-like lesions on your legs that have developed over the past 24 hours. You are very worried about the possible cause and also the appearance – you are getting married in 2 weeks and are worried that it may spread to more conspicuous areas.

Focused history and examination

Initial history

- Ask about symptoms of the shin lesions, notably if they are painful.
- Ask about past medical history and recent illnesses or drugs.

Initial examination

- Be aware of the most likely causes of a shin rash listed below.

Erythema nodosum

There are *erythematous* (progressing through the colour changes of a bruise), *warm, nodular* (flatten with healing) *lesions over the anterior aspect of both shins* (Fig. 5.19). They

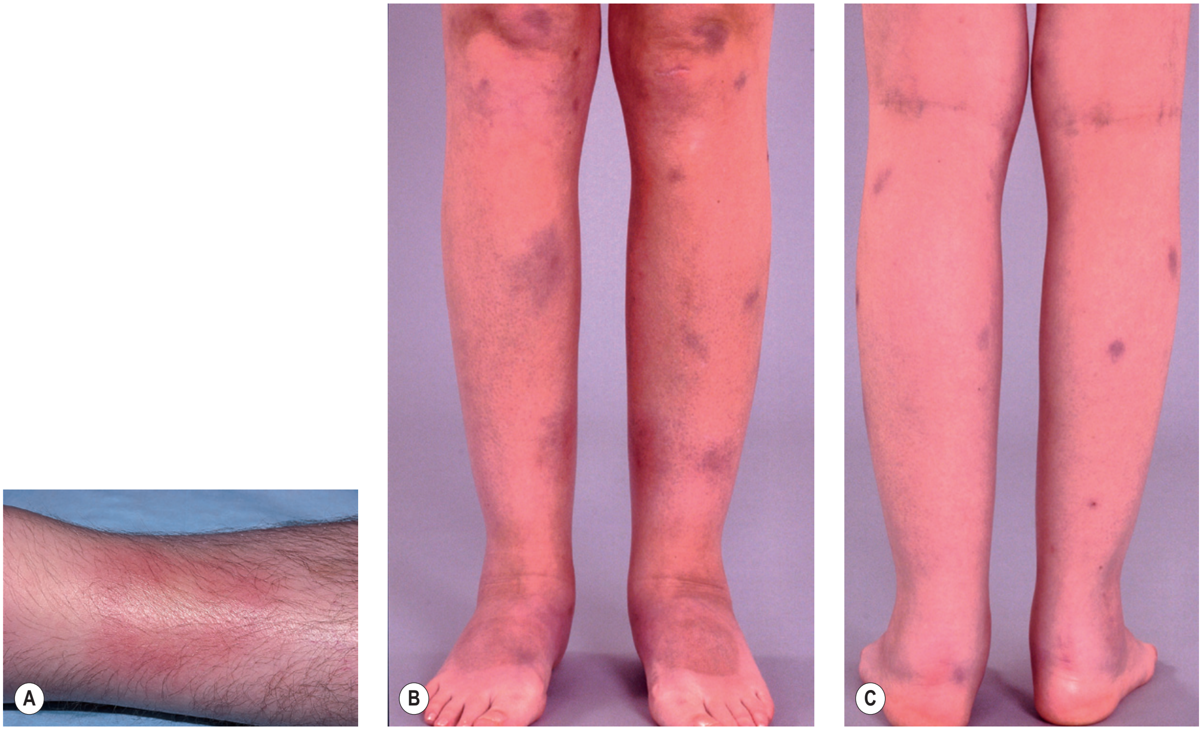


Figure 5.19 (A–C) Erythema nodosum.

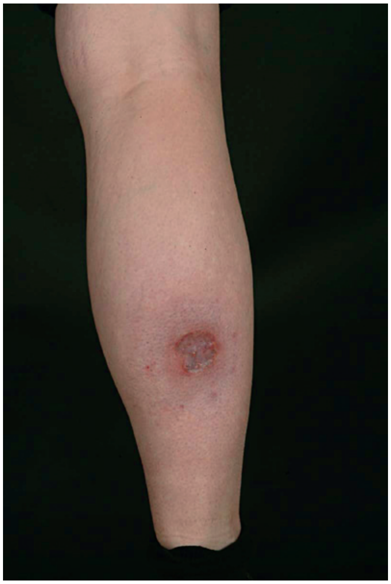


Figure 5.20 Pyoderma gangrenosum.

may be single or multiple, of various sizes, and may occur elsewhere. Ask if they are *tender* (before you examine them!). Lesions evolve slowly, changing from acute red nodules to residual bruises over a period of weeks.

Pyoderma gangrenosum

Several variants of pyoderma gangrenosum exist. *Classic pyoderma gangrenosum* is a *deep ulcer* with a *well-defined border* that is usually violet or blue (Fig. 5.20). The ulcer edge may be undermined (worn and damaged) and the surrounding skin may be erythematous and indurated. The ulcer often starts as a red papule or nodule or collection of papules, which break down to form small ulcers with a 'cat's paw' appearance; these coalesce and the central area becomes necrotic and forms the ulcer. Lesions are painful. Pyoderma gangrenosum can occur at any site, but the face and legs are common sites. Healing often leaves a papery scar.

Variants include *peristomal* pyoderma gangrenosum (around 15% of all cases), *pustular pyoderma gangrenosum* (a rare, superficial variant), *bullous pyoderma gangrenosum* (a superficial variant that tends to affect the upper limbs or face and often associated with haematological malignancy) and *vegetative pyoderma gangrenosum* (a less aggressive superficial form).

Necrobiosis lipoidica (diabeticorum)

There are *well-demarcated (often oval) non-scaling plaques* on the shins (Fig. 5.21). Characteristically they occur on the legs but they may occur anywhere else. They have a *shiny, atrophic surface, red/brown margins* and *yellow waxy centres. Surface telangiectasia* is characteristic. Trauma often results in persistent ulceration (Fig. 5.22).

Table 5.12 Causes of erythema nodosum and pyoderma gangrenosum

	Erythema nodosum	Pyoderma gangrenosum
Infection	Viral *Streptococcus* (sore throat) *Salmonella* or *Campylobacter* (enteritis) Primary tuberculosis Leprosy Fungi	Uncommon, but pyoderma gangrenosum should be in the differential diagnosis of any non-healing ulcer – also consider infection, chronic venous insufficiency, peripheral vascular disease, vasculitis, neuropathy (often with Charcot's joints), sickle cell disease and malignancy
Drugs	Oral contraceptive pill Sulphonamides Tetracyclines Penicillin	Uncommon
Inflammation	Ulcerative colitis Crohn's disease	Ulcerative colitis Crohn's disease
Other systemic disease	Sarcoidosis, commonly with arthralgia and bilateral hilar lymphadenopathy	Rheumatoid arthritis Ankylosing spondylitis Chronic active hepatitis Primary biliary cirrhosis Sclerosing cholangitis Sarcoidosis Diabetes mellitus Thyroid disease
Malignancy	Lymphoma	Lymphoproliferative and myeloproliferative disorders
Other	Pregnancy	

Pretibial myxoedema

There are *elevated symmetrical shin lesions* (Fig. 5.23). Such lesions may occur at other sites. They are *coarse, purplish red or brown*, with *well-defined edges*. The *skin is shiny*, with an *orange peel appearance*. The lesions may be asymptomatic or painful. Coarse hairs tend to occur in the vicinity of the lesions.

Further assessment

- Be aware of the presence of a confirmatory feature (Box 5.5).
- Consider possible causes of erythema nodosum and pyoderma gangrenosum (Table 5.12). Pretibial myxoedema is specific to Graves' disease and the superficial layer of the skin is infiltrated with mucopolysaccharides and hyaluronic acid.

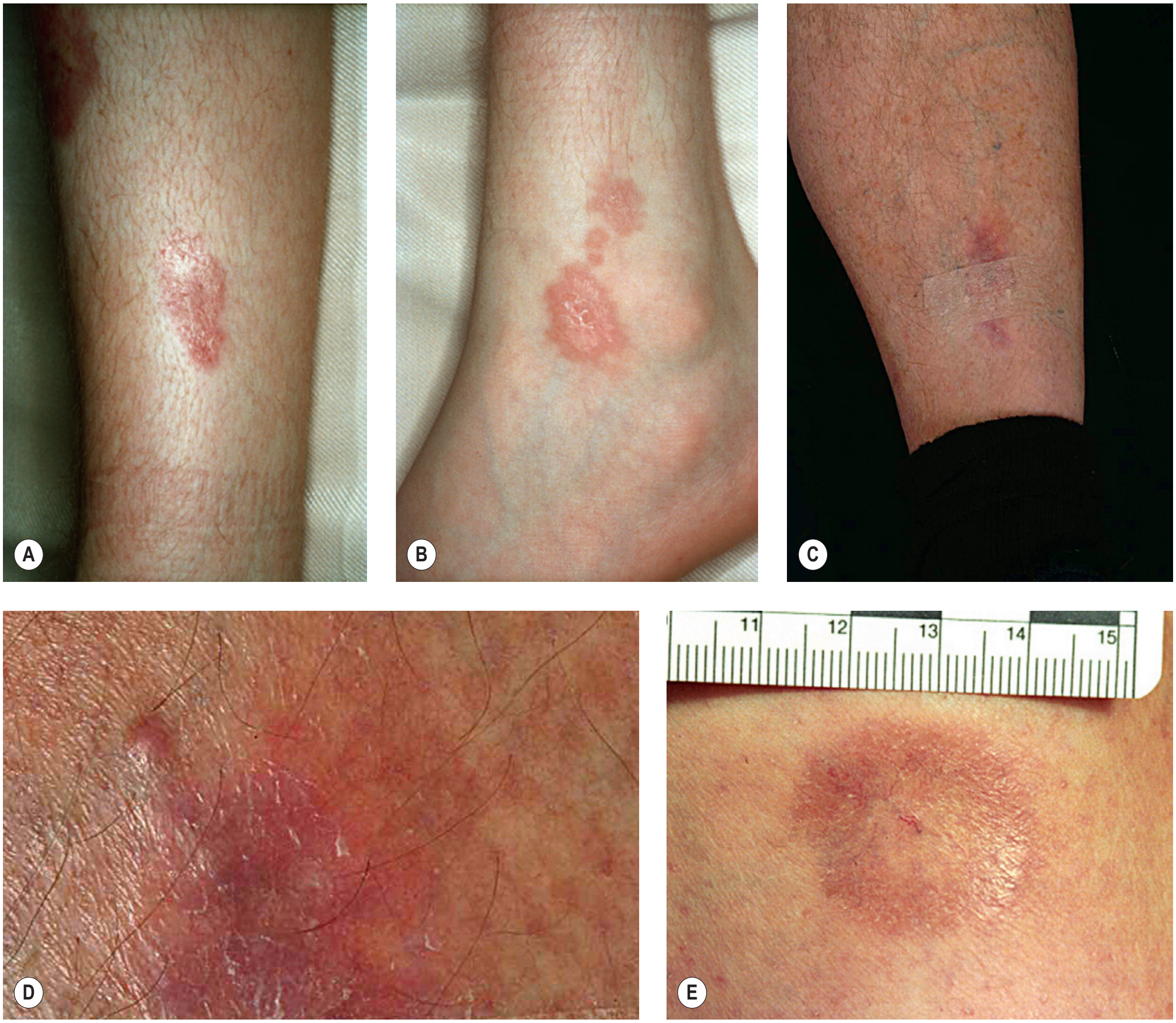


Figure 5.21 (A–E) Necrobiosis lipoidica diabeticorum.

Box 5.5 **Features to help confirm diagnosis of shin lesion**

Erythema nodosum	characteristically tender
Pyoderma gangrenosum	characteristically ulcerated
Necrobiosis lipoidica	characteristically exhibits telangiectasia
Pretibial myxoedema	characteristic 'orange-peel' surface

Necrobiosis lipoidica may occur in diabetes, although it affects < 0.5% of patients and there is, in essence, degeneration and thickening of collagen bundles within the dermis with a palisading granuloma and lesions progress slowly and seldom resolve as there is little effective treatment.

- Explore concerns.

Feedback to patient

This looks like a condition called erythema nodosum. It is not uncommon, and many things can provoke it including throat infections and antibiotics. It should settle down slowly, although it can take few weeks to fully disappear. It is very unlikely to spread

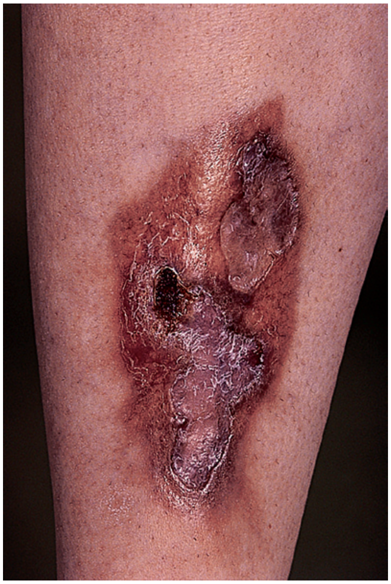


Figure 5.22 Necrobiosis lipoidica diabeticorum – ulcerated.

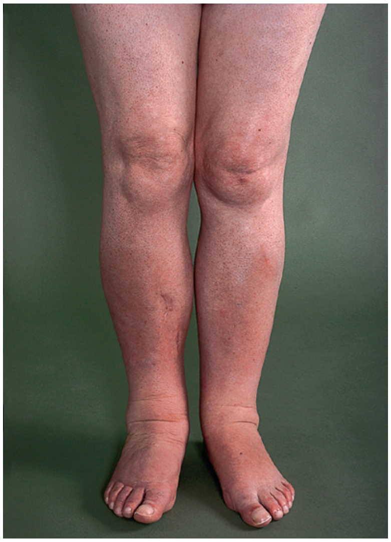


Figure 5.23 Pretibial myxoedema.

elsewhere. It would be a good idea, I feel, to obtain some blood tests and a chest X-ray (always confirm pregnancy status) to make sure there is nothing else afoot but if all is well and symptoms are getting better rather than worse we should be able to send you home with follow-up by your general practitioner. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has tender spontaneous bruise-like lesions on her legs characteristic of erythema nodosum.

Provide a diagnosis or differential diagnosis with supporting evidence

The likely trigger is infection or antibiotics.

Outline an investigation and management plan

It should settle spontaneously, although it would be sensible to arrange blood tests (including clotting) and a chest X-ray to exclude hilar lymphadenopathy.

CASE 5.9 NEUROFIBROMATOSIS AND TUBEROSE SCLEROSIS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mr John Evans, aged 40 years

This man has been admitted to hospital with a first seizure. He has a significant background medical history.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 40-year-old man who has been admitted to hospital with a first seizure. You have neurofibromatosis with café-au-lait spots and freckling and peripheral neurofibromas and Lisch nodules and wonder if the seizure could be related to this condition. You are also concerned because you have not seen anyone about the condition for many years and have numerous concerns such as likely prognosis and how it is inherited.

Focused history and examination

Initial history

- Ask about the seizure symptoms.
- Ask about driving.

Initial examination

- Recognise the neurofibromatosis. There are multiple *café-au-lait spots*, each more than 15 mm in greatest diameter. There is *axillary and skin-fold freckling*. There are multiple *neurofibromas*. These may be soft mobile subcutaneous lumps or nodules along peripheral nerves (Fig. 5.24 and Fig. 5.25 Neurofibromatosis type 1).

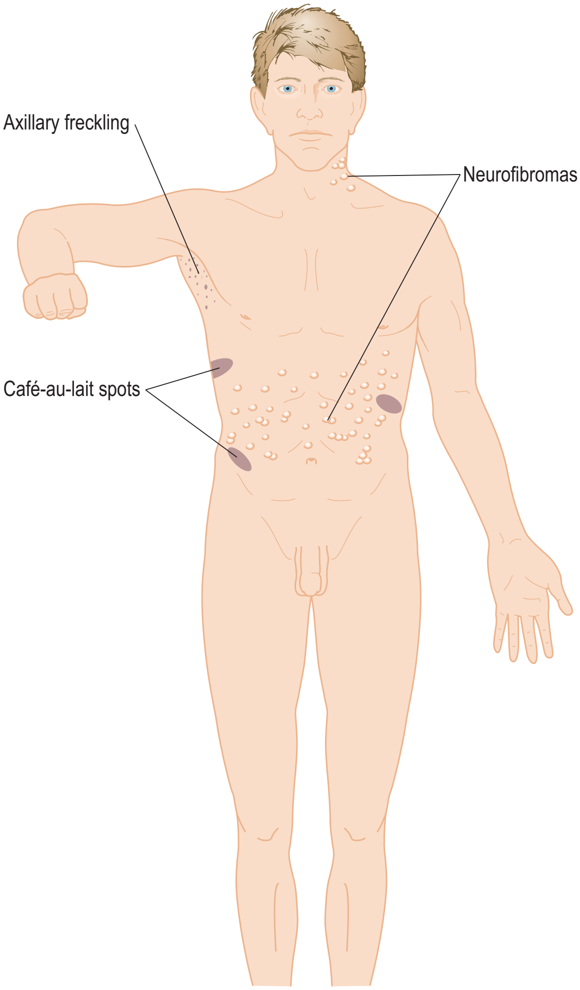


Figure 5.24 Café-au-lait spots, neurofibromas and axillary freckling.

Further assessment

- Explore his concerns. You should have an overview understanding of the neurofibromatoses in order to address his concerns:

Neurofibromatoses are a group of disorders characterised by tumours of the nervous system and characteristic skin pigmentation. There are two types of neurofibromatosis – NF1 and NF2, different at molecular and clinical levels. The type of peripheral nerve tumour (neurofibroma versus schwannoma), the presence or absence of café-au-lait spots and skin-fold freckling and the presence of certain ophthalmic features characterise each type.

Epidemiology

NF1 is one of the most common autosomal dominant conditions, with an incidence of around 1 in 3000 births. Its major features – neurofibromas, café-au-lait spots and Lisch nodules – are not generally associated with other problems. NF2 is much less common with an incidence of around 1 in 30 000 to 1 in 40 000.

Genetic basis

Inheritance of both NF1 and NF2 is autosomal dominant, but about 50% of cases of NF1 and NF2 are first cases within a family; penetrance is 100% by age 5 such that if no café-au-lait spots are present by then it can be inferred that NF1 has not been inherited. Around 10% of people without neurofibromatosis have one or two café-au-lait spots. A small number of people with NF1 have fewer than six spots, and disease can be identified by a positive family history and observation to teenage years for neurofibromas, or by genetic testing. The genes affected in both types normally act as tumour suppressors. The *NF1* gene is on chromosome 17 and encodes the protein neurofibromin, a GTPase-activating protein for the p21 ras protein family that normally inhibits ras by converting active ras-GTP to inactive ras-GDP. Neurofibromin absence thus leads to cell growth activation. The *NF1* gene is large, with many mutations with slightly varying clinical manifestations, whereas *NF2* tends to cause predictable features within a family. The *NF2* gene is on chromosome 22 and encodes the protein merlin (schwannomin – a negative growth regulator affecting cell signalling), part of the Ezrin–Radixin–Moexin (ERM) sub-group of the protein 4.1 super family.

Diagnostic criteria and clinical features

The diagnostic criteria for NF1, based on the 1987 National Institutes of Health consensus, are shown in Box 5.6, as are the Manchester criteria for NF2, although it will not be necessary to know these (nor, indeed, the genetics beyond autosomal dominance, but it is important to keep the geeks happy).

And so NF1 is very much a condition of café-au-lait spots and freckling, peripheral neurofibromas and Lisch nodules, the frequencies of these features are high and are detailed in Table 5.13. Plexiform neurofibromas (fusiform enlargement rather than subcutaneous nodules) are

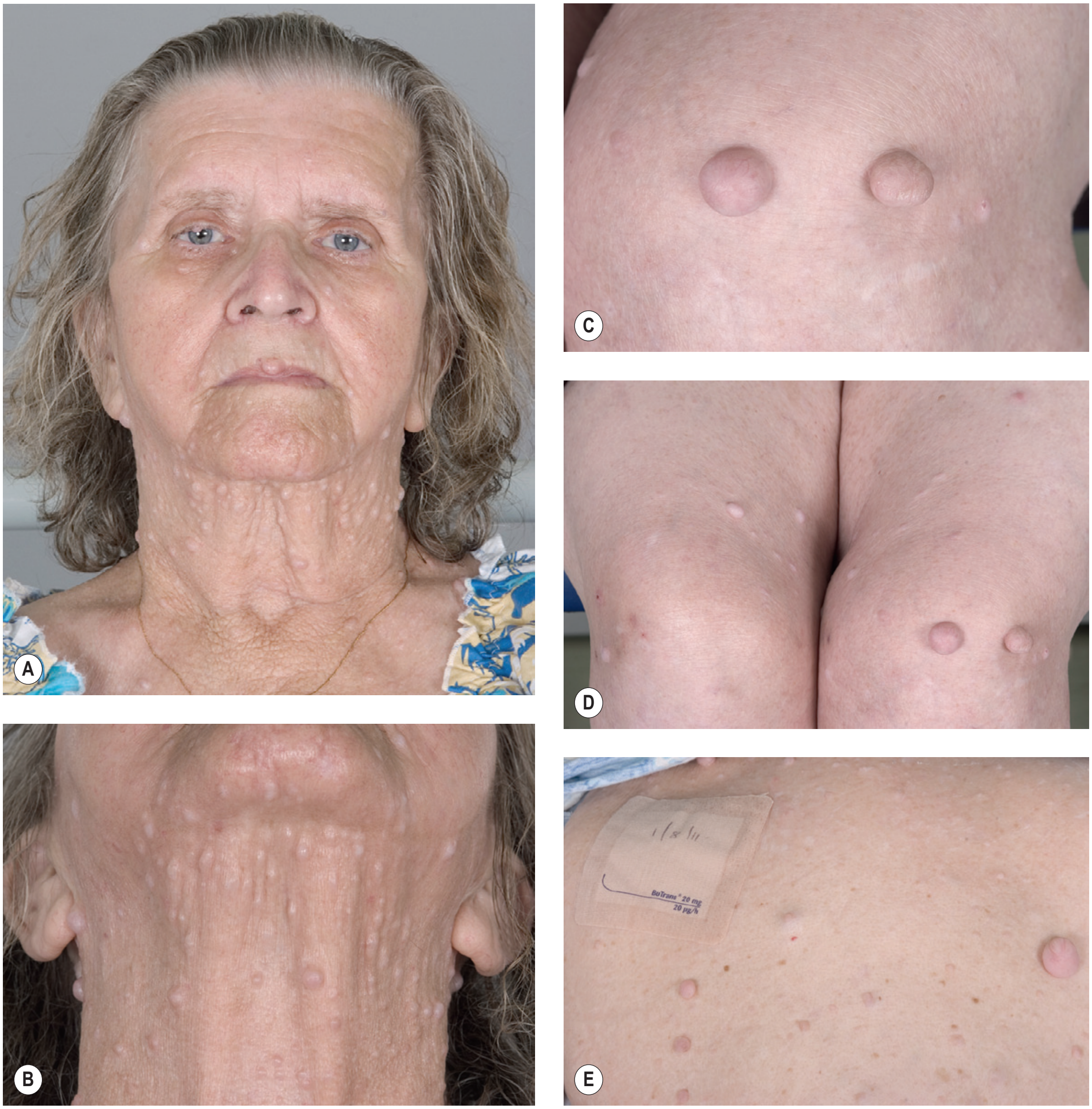


Figure 5.25 Neurofibromatosis type 1.

common and may be large lesions on the head and neck, limb or trunk, associated with skin and bone hypertrophy. Optic gliomas are quite common. Around 50% of people with NF1 develop complications. By far the commonest are learning problems, usually minor. Spinal neurofibromas are not uncommon. Seizures are not that common. All other complications are unusual, with a frequency under 5%. These include aqueduct stenosis, orthopaedic complications (scoliosis, pseudoarthrosis of tibia and fibula, sphenoid wing dysplasia), malignancy and other tumours (malignant peripheral nerve sheath tumours, pelvic rhabdomyosarcomas, gastrointestinal neurofibromas, phaeochromocytomas, duodenal carcinoid, glomus tumours of nail beds), vascular complications (renal artery stenosis, cerebrovascular disease) and interstitial lung disease. Complications cannot be predicted, even within families.

NF2, conversely, is characterised by its hallmark of bilateral vestibular schwannomas (the term preferred to acoustic neuromas here since they are schwannomas histologically arising from the vestibular branch of the eighth nerve). Meningiomas and other cranial nerve and spinal root schwannomas are also common. NF2 does not cause skin-fold freckling, but does cause a unique skin lesion: the NF2 plaque. NF2 also causes ophthalmic complications. NF2 is thus easy to distinguish from NF1, except in

Box 5.6 **Diagnostic criteria for neurofibromatosis**

Diagnostic criteria for neurofibromatosis 1 (NF1)

Two or more of the following are diagnostic:

- Six or more café-au-lait spots (> 5 mm in diameter prepubertal or > 15 mm in diameter postpubertal)
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- Osseous lesion, e.g. sphenoid dysplasia, thinning of long bone cortex
- First-degree relative with NF1 by above criteria.

Diagnostic criteria for neurofibromatosis 2 (NF2)

Any one of the following is diagnostic:

- Bilateral vestibular schwannomas
- First-degree relative with NF2 and unilateral vestibular schwannoma or any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
- Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
- Multiple meningiomas (two or more) and unilateral vestibular schwannoma and any two of: schwannoma, glioma, neurofibroma, cataract.

Table 5.13 Clinical features of neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2)

	NF1				**NF2**	
	Major defining features	**Frequency and significance**			**Major defining features**	**Frequency and significance**
Skin	Café-au-lait spots	> 99% Cosmetic			Café-au-lait spots	≤ 4 (6 very rare) Nearly 50%
	Freckling (skin fold)	> 99% Cosmetic			NF2 plaques	Around 50%
Nerve	Peripheral neurofibromas	Two types, each comprising all elements of a peripheral nerve	Dermal neurofibroma	Most patients have Arise dermis and epidermis Move with skin, discrete, soft, usually asymptomatic No malignant potential	Bilateral vestibular schwannomas	85%
					Meningiomas	45%
			Nodular neurofibroma	5–10% of patients Arise major peripheral nerve, firm Symptoms common Higher risk of malignant peripheral nerve sheath tumours	Peripheral nervous system involvement	70%
					Other, e.g. ependymomas, astrocytomas	
Eye	Lisch nodules	90–95% Cosmetic Melanocytic hamartomas of the iris, appearing as well-defined, yellow-brown, dome-shaped elevations on the surface of the iris			Cataracts (posterior capsular or cortical or both) Retinal hamartomas	80%

a small number of cases of NF2 with a few café-au-lait spots and peripheral nerve tumours indistinguishable from those in NF1. However, histologically these are schwannomas in NF2. Unlike NF1, NF2 is associated with significant morbidity and mortality in all patients.

Differential diagnosis

Another condition, tuberose sclerosis, occasionally appears in PACES. It is also an autosomal dominant condition (*TSC1* gene at 9q34 and *TSC2* gene at 16p13.3) in which hamartomas occur in multiple organs. There are often multiple small skin lesions on the face – flesh coloured or pink papules on the nose and cheeks are *angiofibromata* (Fig. 5.26) (once incorrectly called adenoma sebaceum), very similar to adenoma sebaceum and tending to be symmetrical, e.g. nasolabial folds, butterfly rash. Leathery, lumpy, flesh-coloured *shagreen patches* may be present, often on the trunk. There may also be hypopigmented macules in an oval or mountain ash leaf configuration. Periungual fibromata arise from the proximal nail folds of the fingers or toes. Other organs that can be affected by the hamartomas include the brain (epilepsy, learning dif-

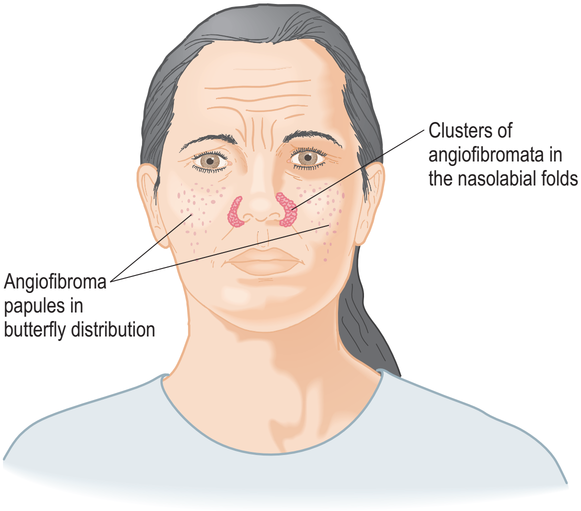

Clusters of angiofibromata in the nasolabial folds
Angiofibroma papules in butterfly distribution

Figure 5.26 Angiofibromata.

ficulties), retina, kidney (cysts), heart, lung (pneumothoraces) and bone.

Feedback to patient

Seizures are not that common in neurofibromatosis and are quite common in the general population and so it is by no means certain that the neurofibromatosis and the seizure are linked. However, just as nerve thickening can occur elsewhere, it is possible for it to occur in the brain. I think we should arrange, as well as blood tests, a magnetic resonance brain scan to look at things in more detail, and seek the advice of a neurologist about whether or not to start medication to prevent further seizures. The main features of your neurofibromatosis are these pale brown spots called café-au-lait spots, freckling, thickening of peripheral nerves known as peripheral neurofibromas, and the nodules in the eye (not always seen) known as Lisch nodules. These features suggest that you have the most common type of neurofibromatosis called NF1. This generally has a much better outlook than the other type of neurofibromatosis, NF2. Both types are inherited with a one in two chance. We could certainly ask an expert in neurofibromatosis – usually a genetics expert – to see you to talk about the condition and its future in more detail. Otherwise I'd be happy to try to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has multiple café-au-lait spots, each more than about 15 mm in greatest diameter. There is axillary and skin-fold freckling. There are multiple neurofibromas.

Provide a diagnosis or differential diagnosis with supporting evidence

He has neurofibromatosis type 1, NF1, much different from NF2, which is characterised by vestibular schwannomas and a greater malignant potential. NF1 can certainly be complicated by minor learning problems and sometimes by seizures, although most other complications are uncommon.

Outline an investigation and management plan

Genetic testing is not routine because clinical diagnosis is usually straightforward and there is a large array of possible genetic mutations. It may be used in prenatal counselling or to establish diagnosis in rare situations where NF1 diagnostic criteria are fulfilled but with very limited evidence of disease (NF1 limited to a segment with just six café-au-lait spots and axillary freckles, known as mosaic NF1 and which may not be inheritable as gonadal tissue may be unaffected, or a rare homozygous recessive disorder of mismatch repair genes in which there are six or more café-au-lait spots and an affected sibling, but no other features).

NF1 management in adults is largely education based, teaching patients about possible complications. NF2 is managed in multidisciplinary specialist centres.

CASE 5.10 NEOPLASTIC SKIN LESIONS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mrs Anna Watson, aged 40 years

This woman is in your outpatient clinic because of diabetes. However, she mentions that she has a skin lesion on her leg.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 40-year-old woman with stable diabetes in the outpatient clinic. You mention to the ward doctor that you have a brown lesion on your leg. It has been enlarging over the past few months. You have spent considerable time in the sun. You are worried about melanoma.

Focused history and examination

Initial history

- Ask about the duration of the lesion.
- Ask about symptoms, e.g. itch, bleeding.
- Ask about any provoking and relieving factors.
- Ask about sunlight exposure – usual or excessive, e.g. outdoor occupation

Initial examination

- Be aware of the wide-ranging skin manifestations of malignancy (Box 5.7).

Box 5.7 **Skin manifestations of malignancy**

Primary skin malignancy

Important skin neoplasms arising in the epidermis are malignant melanoma, squamous cell carcinoma (often with a keratotic surface) and basal cell carcinoma (Fig. 5.27, a rolled pearly edge characteristic, but may be raised red patches, ulcerated and even deeply invasive if untreated but metastases are more likely with malignant melanoma and squamous cell carcinoma). Less common skin tumours arise from blood vessels (e.g. angiosarcoma) or connective tissue (e.g. dermatofibromasarcoma).

Premalignant sun-related lesions

These include solar keratoses, cutaneous horns, actinic chelitis, disseminated superficial actinic parakeratosis and Bowen's disease.

Direct or metastatic spread to skin

The skin is an uncommon site of distant metastases, but primary sites include lung, colon and oral squamous cell cancer.

Paraneoplastic syndromes involving the skin

There is a wide range, e.g. amyloidosis, carcinoid syndrome, cryoglobulinaemia, dermatomyositis, migratory erythema, migratory thrombophlebitis, paraneoplastic pemphigus, pruritus, pyoderma gangrenosum and Sweet's syndrome.

Skin manifestations of haematological malignancy

Itch is common with lymphomas and myeloproliferative disorders. Infections are common, especially in immunocompromised people – bacterial, herpes virus, cytomegalovirus, fungal and yeast infections such as candidiasis and pityriasis versicolor. Autoimmune diseases, notably thrombotic thrombocytopenic purpura, haemolytic anaemia, vitiligo, alopecia, Raynaud's phenomenon and vasculitis, are more common in myelodysplastic syndromes. Drug-induced skin disease is common, such as toxic erythema, and vitiligo around the eyes from tyrosine kinase inhibitors. Neutrophilic dermatoses include pyoderma gangrenosum and Sweet's syndrome (well-defined red or plum-coloured plaques), and may be associated with myeloid leukaemias. Leukaemia cutis is infiltration of neoplastic leucocytes in the skin presenting as deep-red or purple plaques and can occur in acute myeloid leukaemia. Adult T-cell leukaemia/lymphoma associated with human T-cell leukaemic virus type-1 retrovirus infection involves the skin early. Plasma cell disorders including myeloma can cause amyloid deposition in blood vessels leading to purpura.

Pigmented lesions usually imply melanocytic naevi (moles). Non-melanocytic lesions can appear pigmented such as seborrhoeic keratoses or vascular lesions. Blue naevi (well-circumscribed blue nodules) or halo naevi (pigmented lesions with a white 'atoll') are benign. The crucial decision is whether a pigmented lesion could be malignant melanoma, a malignant tumour arising from melanocytes, the pigment-producing cells of the epidermis with high metastatic potential. The incidence continues to rise sharply in white people and it arises on any part of the body, commonly the legs in women and back and trunk in men.

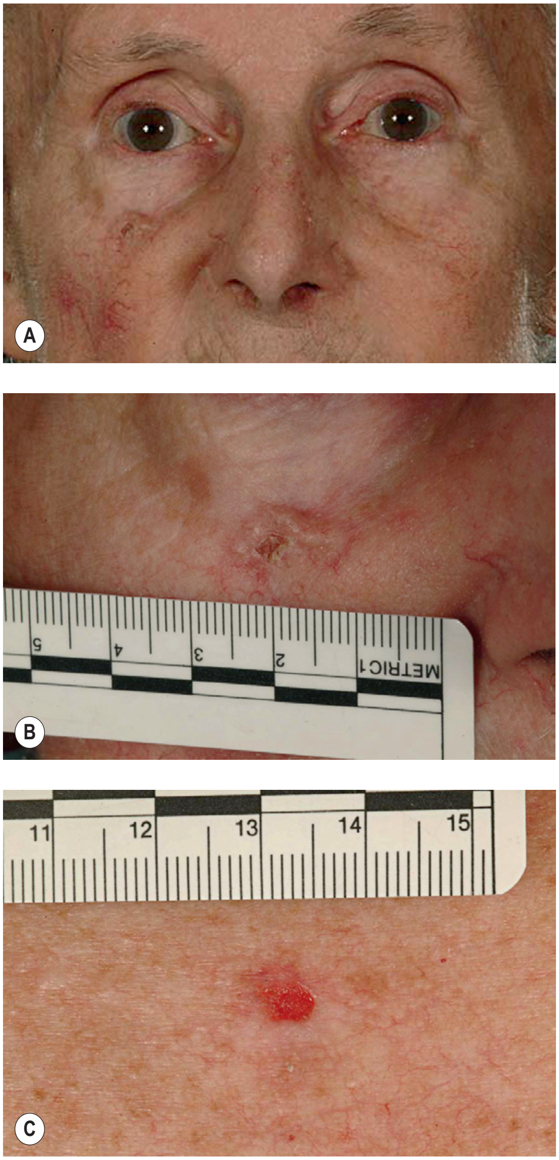


Figure 5.27 (A–C) Basal cell carcinoma.

Table 5.14 Assessing for possible melanoma

Assessment	Features of concern		
Lesions that could be melanoma	New lesion (almost two-thirds of melanomas arise *de novo*), especially over the age of 30 Change in existing mole in size, shape, colour or symptoms		
Risk factors for melanoma	Risk factors include: • Significant sun exposure (ultraviolet exposure in the UK underestimated) – the major risk factor, and while incidence is highest in parts of the world with the longest hours of sunlight, the pattern of exposure is important • Previous sunburns • Type 1 skin (red hair, burns easily, never tans) • Personal or family history of melanoma (family history confers a modestly increased risk) • Immunosuppression. The presence of naevi is the most powerful predictor of risk • (Familial) dysplastic naevus syndrome (atypical naevi are 3–15 mm in diameter with variable colour, and an irregular edge) increases the risk of melanoma • More than 100 common, benign naevi (≤ 2 mm in diameter) or more than two atypical naevi (≥ 5 mm in diameter) carry a five- to 20-fold increased risk • More than 50 atypical naevi increases the risk almost 200-fold. The atypical mole syndrome affects around 2% of the population with a lifetime risk of melanoma of around 1 in 20. Atypical naevi, unlike melanoma, are usually symmetrical and do not have a sharp edge with a geographical border, and remain static, whilst melanoma usually changes in size, shape or colour over months • Congenital naevi, especially giant naevi > 20 cm, carry considerable risk.		
Examination findings	Modified American Cancer Society ABCD system:		
	A	Asymmetry	Divide lesion into four quadrants; asymmetry if lack of mirror image in any of the quadrants
	B	Border	Irregularities of border, with ‘coves’ resembling a coast or place to port a boat; this geographical border has a sharp cut-off from normal skin
	C	Colour variation	≥ 2 colours within lesion Lack of even pigmentation throughout Blue or black pigment highly suspicious; rarely non-pigmented red nodule, more likely on hands or feet
	D	Diameter	> 6 mm in diameter (or any change in size over weeks or months)
	(E)	Evolution of lesion / elevation / erythema	Definite change in size, shape or colour

- Ask whether the lesion has changed, ask about risk factors, and perform ABCDE examination (Table 5.14).

Further assessment

Types of melanoma are listed in Table 5.15. The mean age of presentation is 55 years, but this may depend on the thickness and histological subtype; superficial spreading melanomas, usually thinner, are more common in younger people and nodular melanoma and lentigo maligna melanoma in older individuals.

- Explore concerns.

Feedback to patient

You certainly have a pigmented lesion on the leg. The vast majority of pigmented lesions (all commonly referred to as moles) are either known as benign naevi or atypical naevi. There are a number of features that make a naevus or mole atypical, including colour variation. However, the concern is always whether or not an atypical naevus might be a melanoma. This mole of yours looks small and has irregular colouring within it and a slightly irregular edge. The most compelling reason to have it removed is that, although it is small, it has changed in size. I think we should arrange for you to be seen in our pigmented lesion clinic in the very near future to have it removed, if you are in agreement. That would hopefully be the fastest way too, to build in reassurance, and in the event that it were cancerous then it would hopefully have been removed in entirety before causing any complications. I’d be happy to discuss any further concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has a pigmented lesion on her leg with a number of features of concern – asymmetry, irregular edge, colour variation and evolution in size.

Table 5.15 Types of melanoma

Type	Features
Superficial spreading and nodular melanoma	Commonly history of change in size, shape or colour of pre-existing mole or freckle May arise *de novo* Usually asymmetrical, irregular border, contain more then one colour and over 6.0 mm diameter May be inflamed, crusty, ulcerated or bleeding
Lentigo maligna and lentigo maligna melanoma	Typically sun-exposed areas of face in older people Resembles large, irregular freckle Tends to grow slowly May be regarded as malignant melanoma *in situ* Malignant transformation to invasive lentigo melanoma uncommon, but can occur at any time with prognosis then as for any other melanoma
Acral lentiginous melanoma	Non-hair-bearing skin of soles and palms and under nails (subungual melanoma) Often late diagnosis
Amelanocytic melanoma	Melanoma without pigment Often mistaken for squamous cell carcinoma or pyogenic granuloma

The leg is also a common site for melanoma in women.

Provide a diagnosis or differential diagnosis with supporting evidence

Melanoma must be excluded, but it could simply be an atypical naevus.

Outline an investigation and management plan

It should be removed in the pigmented lesion clinic as soon as possible. Suspicious lesions are excised under a maximum 2-week wait system and if histologically confirmed as melanoma a wider excision is then performed.

Prognosis in melanoma directly relates to depth of invasion, measured histologically from the cornified layer to the deepest invading malignant cell – the Breslow thickness. Sentinel lymph node biopsy also adds prognostic information.

Surgical excision is the only curative treatment but if caught early melanoma has an excellent prognosis, a Breslow thickness under 1 mm, a 5-year survival of 95–100%.

For prevention, avoidance of sunburn, and the sun between the most risky hours of 11 am and 3 pm, are crucial, as are public health measures such as the Slip–Slop–Slap campaign in Australia in the 1990s – slip on a shirt, slop on some sunscreen and slap on a hat. For a condition that is common (about 1 in 100 people have melanoma), curative if detected early and relatively easy to detect (skin examination), screening might seem logical although it would need to be undertaken regularly; currently only high-risk people are screened, and privately funded clinics offering skin photography with computerised annual comparisons of lesions are sparsely available.

Since melanoma may sometimes have a radial growth phase for years during which there is a 95% chance of cure, until or unless national screening occurs, opportunism when examining the trunks of patients should be pursued, to try to catch lesions before the vertical growth phase.

Rheumatological problems

Examination of the joints

EXAMINATION OF THE JOINTS – OVERVIEW

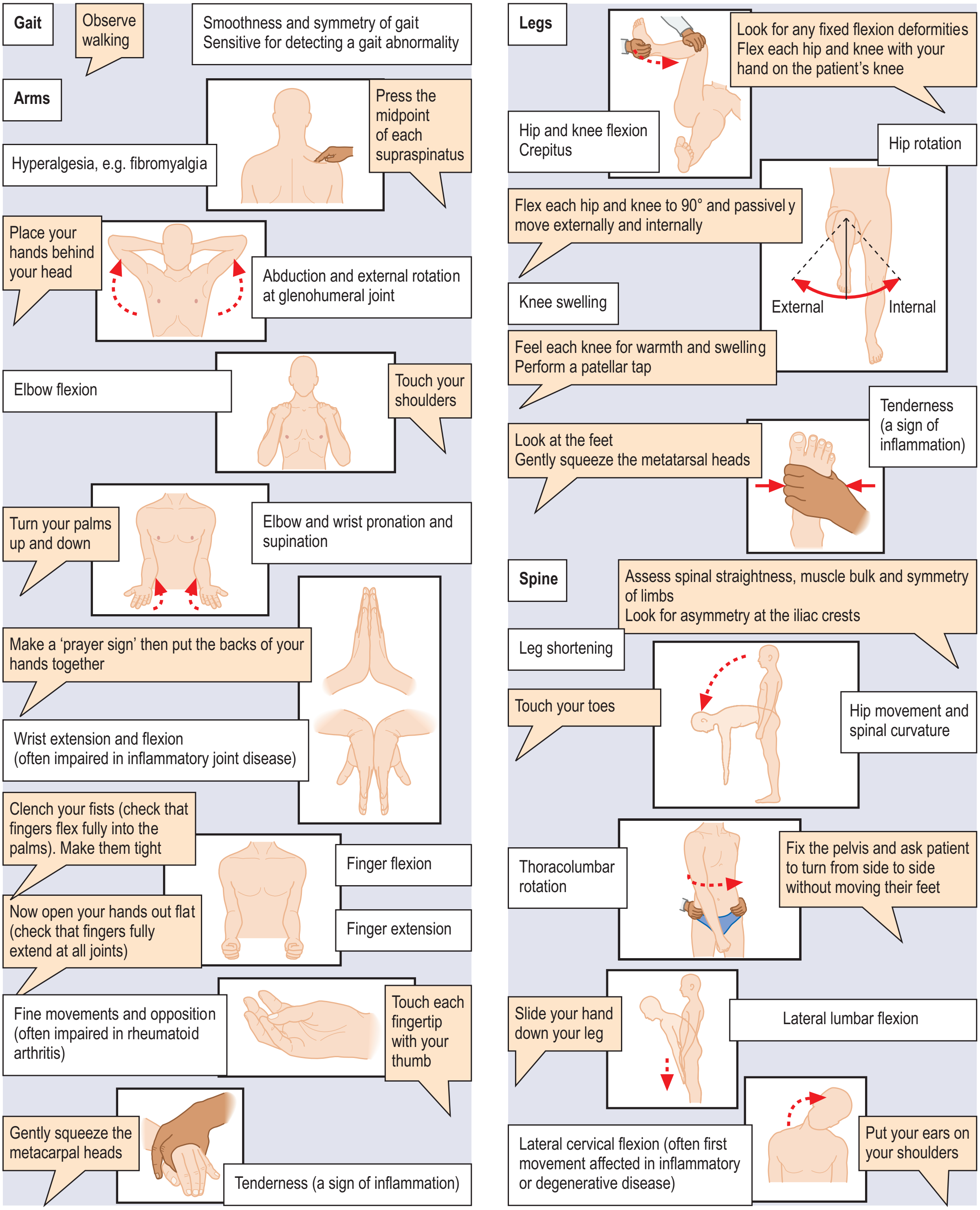
The GALS screen

The locomotor system comprises bones, joints and muscles with associated ligaments, tendons and bursae. A gait, arms, legs, spine (GALS) screen (Fig. 5.28) is useful for rapidly detecting most musculoskeletal problems and some neurological problems, and assesses function. Appearances and movements are recorded. Abnormalities should prompt a full regional examination. Most physicians have developed their own GALS screen.

Regional examination

In PACES you are most likely to be asked to perform a regional examination. This is most commonly of the hands and wrists, but you should be prepared to examine the shoulders, ankles and feet, knees, hips or spine. Regional examination should follow the look–feel–move format (Table 5.16).

Joints may be flexed, extended, abducted, adducted, externally rotated, internally rotated, supinated, pronated, inverted, everted, and circumducted; only ball and socket joints (hip and shoulder) can do the last. In general, pain and stiffness due to synovitis occur with both active and passive movements; pain due to tendonitis is worse with active movements; pain due to movements of a tendon over an inflamed bursa (e.g. impingement in subacromial bursitis) occurs with passive and active movements.



Gait

Observe walking

Smoothness and symmetry of gait
Sensitive for detecting a gait abnormality

Arms

Press the midpoint of each supraspinatus

Hyperalgesia, e.g. fibromyalgia

Place your hands behind your head

Abduction and external rotation at glenohumeral joint

Touch your shoulders

Elbow flexion

Turn your palms up and down

Elbow and wrist pronation and supination

Make a 'prayer sign' then put the backs of your hands together

Wrist extension and flexion
(often impaired in inflammatory joint disease)

Clench your fists (check that fingers flex fully into the palms). Make them tight

Finger flexion

Now open your hands out flat (check that fingers fully extend at all joints)

Finger extension

Touch each fingertip with your thumb

Fine movements and opposition (often impaired in rheumatoid arthritis)

Gently squeeze the metacarpal heads

Tenderness (a sign of inflammation)

Legs

Look for any fixed flexion deformities
Flex each hip and knee with your hand on the patient's knee

Hip and knee flexion
Crepitus

Hip rotation

Flex each hip and knee to 90° and passively move externally and internally

Knee swelling

Feel each knee for warmth and swelling
Perform a patellar tap

Tenderness (a sign of inflammation)

Look at the feet
Gently squeeze the metatarsal heads

Spine

Assess spinal straightness, muscle bulk and symmetry of limbs
Look for asymmetry at the iliac crests

Leg shortening

Touch your toes

Hip movement and spinal curvature

Thoracolumbar rotation

Fix the pelvis and ask patient to turn from side to side without moving their feet

Slide your hand down your leg

Lateral lumbar flexion

Put your ears on your shoulders

Lateral cervical flexion (often first movement affected in inflammatory or degenerative disease)

Figure 5.28 The GALS (gait, arms, legs, spine) screen. Arrowed captions, what to do / instructions to the patient; white text captions, what it tests / detects.

Further assessment

Symptoms

Common rheumatological symptoms are pain, stiffness and joint swelling (Table 5.17).

Autoimmune tests

Diagnosis in autoimmune rheumatic disease may take time, the clinical picture often emerging over months or even years. The detection of autoantibodies to a variety of antigenic targets plays an important role in the diagnosis of autoimmune rheumatic disease. When the history and examination meet a number of diagnostic criteria, autoantibody tests can seek to confirm the diagnosis. This is the purest view, but in practice tests are often requested in the absence of clinical assessment meeting defined criteria. For example, an 18-year-old woman might develop pericarditis as the first manifestation of systemic lupus erythematosus (SLE), and positive autoantibodies are then highly suspicious. Rheumatoid factor, antinuclear antibodies and antineutrophil cytoplasmic antibodies have been the key in the diagnosis of rheumatoid arthritis (RA), SLE and systemic vasculitis for many years. Antibodies against cyclic citrullinated peptides are specific for RA and may predict development of erosive disease and are increasingly used in RA assessment. There is increasing interest in the use of anti-C1q antibodies in detecting and monitoring lupus nephritis as this assay appears to be more sensitive than anti-DNA antibodies. Enzyme-linked immunosorbent assays (ELISAs) are now being used in place of both radioimmunoassay and immunofluorescence because they are readily automated and less dependent on experienced technicians.

Antinuclear antibodies (ANAs) are autoantibodies (usually immunoglobulin G) directed against cellular proteins or nucleic acids; despite their name, several of these antigens are confined to the cytoplasm. The most common ANAs react with DNA–protein or RNA–protein complexes. Immunofluorescence staining (though ELISA is increasingly used) may show a predominantly homogeneous (e.g. SLE – double-stranded DNA), speckled (e.g. Sjögren's syndrome – Ro, La; mixed connective tissue disease – U1RNP), nucleolar (scleroderma – Scl-70) or centromere (scleroderma) pattern. A titre ≥ 1 : 160 is regarded as high. Subsequent detection of antibodies to extractable nuclear antigens is useful in diagnosing specific diseases (Table 5.18).

Table 5.16 Look – feel – move

Look	At the skin, e.g. erythema, scars
	For swellings
	For deformities, e.g. joints, shape and position of the limbs and digits
	For muscle wasting
Feel	The skin (warmth) and surrounding tissues (fluid, soft tissue or bone)
	The joints (at rest)
Move	The joints Movements may be *active* (involving active muscle contraction) or *passive* (especially if active movement limited)

Table 5.17 Differentiating rheumatological disorders by symptoms

Symptoms	Causes	
Diffuse pain not localised to joints and without stiffness	Chronic pain syndrome (Polymyalgia rheumatica causes diffuse symptoms but is characterised by stiffness)	
Pain and stiffness localised to joints without joint swelling (Arthralgia without arthritis)	Osteoarthritis Systemic lupus erythematosus Viral infections (Tendonitis may give rise to pain in the region of a joint, and bursitis to swelling in the region of a joint)	
Pain and stiffness with joint swelling (Arthralgia with arthritis / synovitis)	Monoarticular swelling	Palindromic rheumatoid, usually short lived (days) and occasionally the first manifestation Crystal arthropathy Spondyloarthropathy Septic arthritis Osteoarthritis
	Polyarticular symptoms	Rheumatoid arthritis Crystal arthropathy Spondyloarthropathy Systemic lupus erythematosus Viral infections

Table 5.18 Autoantibody tests

Disease	Autoantibodies to ENAs	Prevalence in this disease (%)	Specificity	Clinical associations
Systemic lupus erythematosus (SLE)	Double-stranded DNA	70	High (unlike antibodies to single-stranded DNA)	SLE Lupus nephritis
	Sm and r ribonucleoprotein	5–15 (30–50 Sm positive if Afro-Caribbean)	High	Central nervous system lupus

Table 5.18 Autoantibody tests—cont'd

Disease	Autoantibodies to ENAs	Prevalence in this disease (%)	Specificity	Clinical associations
	C1q	40	Moderate / high	Lupus nephritis
	Ro (SS-A) La (SS-B)	40 15	High	Sjögren's syndrome, congenital heart block
	Phospholipid	30–40	Low	Antiphospholipid syndrome
Scleroderma / systemic sclerosis (SSc)	Topoisomerase 1 (Scl-70)	30	High	Diffuse cutaneous SSc
	Centromere	60	Moderate	Limited cutaneous SSc
	PM-Scl	5	High	Scleroderma / polymyositis overlap disease (rare)
Sjögren's syndrome	Ro (SS-A)	75	High SSA positive before SSB because SSA peripheral to SSB and exposed to autoantibodies first	Not predictive of particular features but tendency for extraglandular disease
	La (SS-B)	50		
Polymyositis	Jo-1 (a tRNA synthetase)	30	High	Myositis, interstitial lung disease, Raynaud's phenomenon
	Signal recognition peptide	5	High	Severe myositis
	Mi-2	10	High	Dermatomyositis
Mixed connective tissue disease	Small nuclear ribonucleoprotein-70 (snRNP70, also known as U1RNP70)	30	Moderate / high	Overlap / mixed connective tissue disease – features of SLE, scleroderma and rheumatoid arthritis (sometimes polymyositis)
Vasculitis	PR3 (associated with cANCA) MPO (associated with pANCA)	90 50	High Moderate	Wegener's granulomatosis Microscopic polyarteritis Churg–Strauss syndrome

ENA, extractable nuclear antigen.

EXAMINATION OF THE HANDS AND ARMS

The hands and wrists

- Be careful before shaking a patient's hand. Ask if there is pain before examining, and preferably examine the hands rested on a pillow on your seated patient's lap.
- Proceed to look, feel and move (Table 5.19; Figs 5.29 and 5.30).

Swelling, tenderness and crepitus are found over the tendon sheaths in stenosing tenosynovitis (trigger finger), usually a consequence of persistent inflammation. De Quervain's tenosynovitis is a form that affects abductor pollicis longus and extensor pollicis brevis, with symptoms around the base of the thumb and pain aggravated by movements at the wrist or thumb, often with marked crepitus. Osteoarthritis of the carpometacarpal joint may cause similar pain. Finkelstein's test is positive in De Quervain's tenosynovitis – the wrist is deviated in an ulnar direction whilst the thumb is held flexed in the palm by the fingers (Fig. 5.31). This causes pain.

In osteoarthritis, grinding the extended thumb causes pain at the thumb base.

The elbow

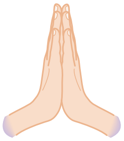
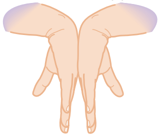
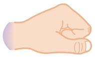
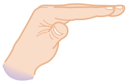
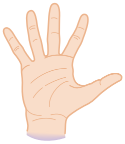
- Ask about any pain.
- Proceed to look, feel and move (Table 5.20).

The shoulder

To know what you are examining for, you should be aware of shoulder joint anatomy (Fig. 5.32). It comprises the glenohumeral joint and the acromioclavicular joint, but movement of the shoulder is also facilitated if the scapula rotates outwards against the chest wall, notably in shoulder abduction. The subacromial joint beneath the acromial head of the scapula is sometimes called the subacromial bursa. Shoulder movements can also move the sternoclavicular joint.

Shoulder problems arise from any of these joints. Common glenohumeral joint problems are adhesive capsulitis and osteoarthritis. A common subacromial joint problem is rotator cuff disease.

Table 5.19 Examining the hands and wrists

Look	At the skin	Erythema suggests acute inflammation, e.g. crystal arthropathy, septic arthritis, tendon sheath infection, soft-tissue infection Look for palmar erythema, vasculitis, digital ischaemia, telangiectasia, purpura (corticosteroids) or scars (arthrodeses or previous carpal tunnel release) Look at the nails for pitting or evidence of vasculitis – nail-fold erythema or infarction		
	For swellings	Swelling of the IP joints or MCP joints suggests synovitis; there is loss of interdigital indentation of the MCP and IP joints when the fingers are flexed ('loss of mountains' sign)		
	For deformities	Swan neck and boutonnière deformities, Z-shaped thumbs and ulnar deviation of the MCP joints are typical of rheumatoid arthritis Anterior (volar) displacement of the wrist from partial dislocation (subluxation) is also common in rheumatoid arthritis A mallet finger or thumb, in which the terminal phalanx cannot be actively extended, is caused by rupture of the extensor tendon, usually from trauma or rheumatoid arthritis Arachnodactyly suggests Marfan's syndrome		
	For muscle wasting	Look for wasting of the thenar or hypothenar muscle groups or both		
Feel	The skin and surrounding tissues	Feel for warmth		
	The joints (at rest)	Bony swellings of the distal or proximal IP joints are likely Heberden's or Bouchard's nodes of osteoarthritis 'Squaring' of the wrist is due to osteophytes at the first CMC joint Soft-tissue swelling suggests synovitis, a fusiform swelling Feel the flexor tendon sheaths for localised swelling or tenderness; if present look for triggering or locking during extension Feel for crepitus of the opening and closing fingers with your index finger		
Move	The joints	Make a 'prayer sign' 		Test wrist extension to 90°
		Now do the opposite 		Test wrist flexion to 90°
		Make a fist Now tighten it 	Note that flexion of the MCP rather than the IP joints is better tested as shown below 	Test finger flexion Incomplete fist formation may be due to a problem with the IP or MCP joints or thickening of the flexor tendons – asking the patient to grip your fingers may detect thickening that is not visible
		Spread your fingers apart 		Test the extensor tendons

CMC, carpometacarpal; IP, interphalangeal; MCP, metacarpophalangeal.

- Ask the patient to point to any site of pain, although this is not a reliable guide for localising the structure from which it arises. Shoulder pain may be referred from cervical roots, thoracic viscera and from structures adjacent to the diaphragm. Patterns of stiffness or loss of movement are more helpful diagnostically; the removal of a garment requires external rotation at the glenohumeral joint, for example.
- Proceed to look, feel and move (Table 5.21).

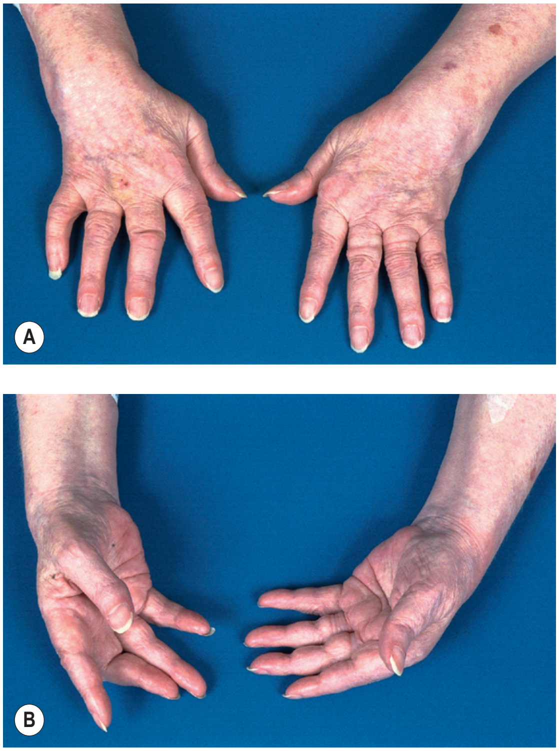


Figure 5.29 Rheumatoid hands – synovitis.

Subacromial disease – rotator cuff disease

This is common under 50 years of age, often *de novo* or due to repetitive strain. The rotator cuff tendons may tear, often partially, or become inflamed, and often a combination of tearing and inflammation gives rise to symptoms. Chronic inflammation in rheumatoid arthritis can also lead to atrophy of the rotator cuff muscles, with symptoms. The rotator cuff muscles and tendons are:

- *Supraspinatus* – allows abduction and elevation of the shoulder via the deltoid
- *Infraspinatus* – allows external rotation of the shoulder
- *Subscapularis* – allows internal rotation of the shoulder.

Supraspinatus tendonitis is the most common problem. Rotator cuff tears tend to cause pain at the deltoid insertion, often worse at night, with weakness of overhead activity and outreach fatigue. There may be wasting of rotator cuff muscles over the scapula (supraspinatus and infraspinatus) and restricted movement, particularly active movement. The rotator cuff, notably supraspinatus, initiates abduction. Its presence between the glenohumeral and subacromial joints means that during abduction of the humeral head the tendon has to slide under the acromion where it rubs against the bony undersurface of the latter. Any tear or damage or focus of inflammation in the tendon will be exacerbated by the constant rubbing against bone, and a vicious cycle is set up. Because of the

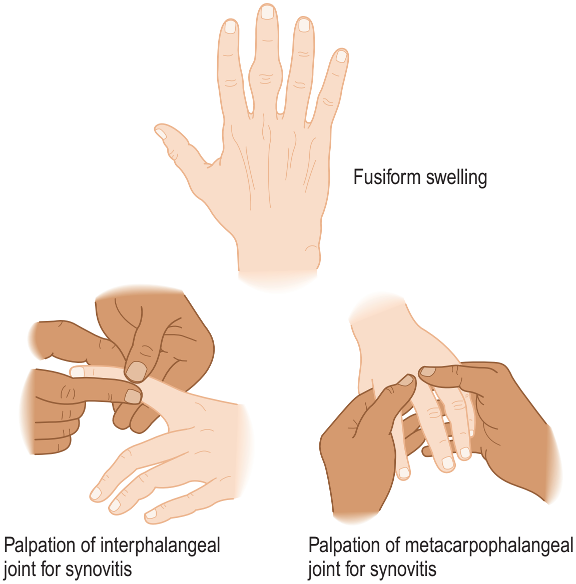

Fusiform swelling
Palpation of interphalangeal joint for synovitis
Palpation of metacarpophalangeal joint for synovitis

Figure 5.30 Examining for synovitis. Press both sides of the joint with the index finger and thumb of one hand and any swelling will 'bulge up'. Now press on the swelling (it has a spongy feel) with the fingers of your other hand. You should normally be able to feel the bony margins of each metacarpophalangeal joint and the gaps between them, especially when the patient makes a fist, like mountain peaks and valleys. In inflammatory joint disease the valleys are filled with synovial fluid.

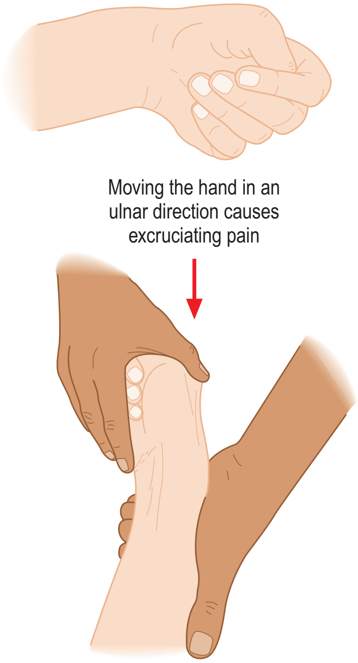

Moving the hand in an ulnar direction causes excruciating pain

Figure 5.31 Finkelstein's test.

restricted space, the tendon may reach a point of being stuck ('impingement'), particularly as the humeral head and acromion come together. But once the tendon has passed through the space, the remainder of abduction is painless and easier. This contrasts with acromioclavicular joint disease, usually more symptomatic with high arc abduction. Plain X-rays may show tendon calcification, and atrophy demonstrated by subacromial space narrowing (decreased vertical height between the humeral head and the acromion). Ultrasound or magnetic resonance imaging is helpful. Treatments include steroid injections, physiotherapy and surgery, although a degree of rotator cuff pathology is almost inevitable in most people at some stage, not necessarily symptomatic.

Table 5.20 Examining the elbow

Look	At the skin	Look for rheumatoid nodules or psoriatic plaques
	For swellings	Synovitis or an effusion appears as a bulge between the olecranon and the lateral epicondyle Look for olecranon bursitis
	For deformities	Look for any valgus or varus deformity
	For muscle wasting	
Feel	The skin and surrounding tissues	Feel for bursitis Feel for rheumatoid nodules Feel for focal tenderness, laterally for a lateral (tennis elbow) epicondylitis causing pain over the lateral elbow and forearm and medially for a medial (golfer's elbow) epicondylitis causing pain over the medial elbow and forearm
	The joints (at rest)	Feel the bony contours of the elbow Feel for synovitis
Move	The joints	Flex and extend the joint, and feel for crepitus Test supination and pronation

Glenohumeral disease – adhesive capsulitis ('frozen shoulder') and osteoarthritis

Distinguishing these two common differential diagnoses is outlined in Table 5.22.

Summary

A summary of the hands and arms examination sequence is in the Summary box.

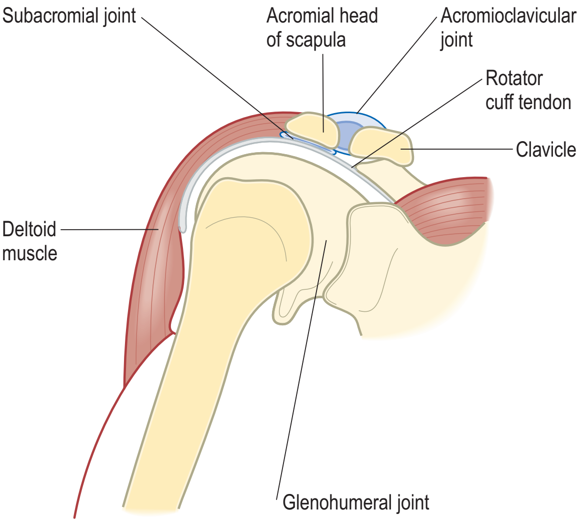


Figure 5.32 The shoulder.

Table 5.21 Examining the shoulder

Look	At the skin	Erythema and signs of inflammation are rare
	For swellings	Although swelling is unusual, rotator cuff tears with bleeds, rheumatoid arthritis effusions, pseudogout and sepsis can all affect the shoulder. A chronic effusion occurs in a peculiar destructive apatite arthritis of the shoulder (Milwaukee shoulder)
	For deformities	Anterior glenohumeral dislocation (depressed shoulder) and complete acromioclavicular joint dislocation (elevated acromion) are usually obvious, but posterior dislocation can be subtle Elevated or depressed scapulae occur in rare syndromes. Winging of the scapula suggests paralysis of the nerve to serratus anterior
	For muscle wasting	Look at the shoulder contours, especially at the supraspinatus and infraspinatus muscles overlying the upper and lower segments of the scapula; flattening suggests rotator cuff muscle atrophy due to a chronic tear in their tendons
Feel	The skin and surrounding tissues	Feel the supraspinatus tendon by extending the shoulder to bring supraspinatus anterior to the acromion process
	The joint (at rest)	Feel from the sternoclavicular joint and along the clavicle to the acromioclavicular joint. Clavicular or acromioclavicular fractures produce deformity and tenderness Feel the acromion and scapula spine Feel the glenohumeral joint by feeling for the humeral head and sliding your finger into the anterior groove, which is tender in a capsulitis but not in osteoarthritis

Table 5.21 Examining the shoulder—cont'd

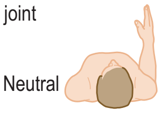
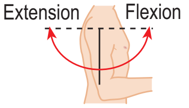
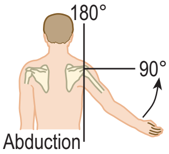
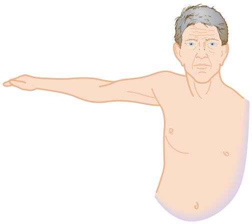
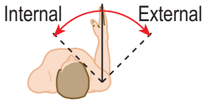
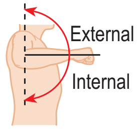
Move	The joint  	As a screening test stand behind the patient and ask them to put their hands behind their head and then their hands behind their back reaching upwards to touch their shoulder blades Pain or limited movement warrant full examination		
	 Flexion and extension	Ask the patient to flex and extend the shoulder as far as possible		
	 	Test the abduction arcs by asking the patient to abduct the shoulder in the neutral (palm to leg) position  Normally the scapula swings out and rotates on the chest wall after about 70° of abduction, but the first 70° requires the glenohumeral joint alone	Rotator cuff lesions	Pain and restricted movement, especially active movement May be exacerbated by gentle resistance Pain starting in early abduction very suggestive, around 40° to 120°
			Glenohumeral joint disease, usually a capsulitis	Scapular movement starts early, confirmed by palpating the inferior border of the scapula whilst patient abducts
	 Rotation		Acromioclavicular arthritis	Pain during a high arc of movement (even passive) – 90° to 180°
	 Rotation in abduction	Test active external rotation, a function of the rotator cuff and painful and restricted in rotator cuff disease – returning to the neutral position with elbows flexed at 90° and held at the side, place your hands outside the patient's and ask them to push their hands outwards whilst keeping their elbows tucked in		

Table 5.22 Glenohumeral disease – adhesive capsulitis versus osteoarthritis

	Adhesive capsulitis	**Osteoarthritis**
Age	Uncommon under 40 Peak 56	Older people Less common than adhesive capsulitis
Pathology	Fibrosis	Degeneration and osteophytes
Symptoms	Severe pain, often worse at night Insidious stiffness, often over several months	Pain Stiffness
Signs	Near complete loss of passive and active external rotation (hands behind head) of the shoulder The arm is held in adduction and internal rotation	Stiff, often creaky joint
Progress	Three clinical phases 1. Painful freezing (lasts 3–9 months) 2. Adhesive phase (lasts 4–12 months) 3. Resolution phase (lasts 12–24 months)	Can wax and wane
Investigations	Diagnosis is clinical	Plain radiograph
Treatment	NSAIDs are often ineffective. Steroid injections and physiotherapy are used in the painful freezing phase Manipulation under anaesthesia and surgical release occasionally warranted in the adhesive phase	NSAIDs Steroid injections Physiotherapy Surgery
Prognosis	Mean duration 30 months	Slowly progresses

NSAID, non-steroidal anti-inflammatory drug.

SUMMARY BOX – HANDS AND ARMS EXAMINATION SEQUENCE

For each region:
- ◆ Look at the skin
- ◆ Look for swellings
- ◆ Look for deformities
- ◆ Look for muscle wasting
- ◆ Feel the skin and surrounding tissues
- ◆ Feel the joints at rest
- ◆ Move the joints.

EXAMINATION OF THE LEGS

The hip

The hips are less likely to be involved in inflammatory arthritis and are usually a source of pain, rather than swelling, that is often referred to the groin or downward to the knee.

- Ask whether there is pain.
- Proceed to look, feel and move (Table 5.23).

Thomas's test

A flexion deformity of the hip can be masked if the patient tilts the pelvis forwards and increases the lumbar lordosis. Thomas's test can be used to obliterate the lumbar lordosis and unmask hip flexion (Fig. 5.33). The unaffected hip is flexed to its limit (do not do this if there is a hip replacement, as it may dislocate) to straighten the lumbar spine. An affected hip rises from the couch to reveal the degree of abnormal flexion.

Trendelenberg's test

Standing on one leg on the side of a diseased hip may cause the contralateral hemipelvis to fall below the horizontal.

The knee

- Ask whether there is pain.
- Proceed to look, feel and move (Table 5.24).

Table 5.23 Examining the hip

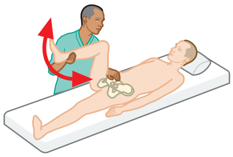
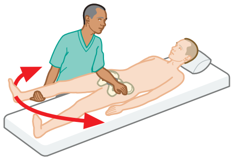
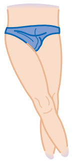
Look	At the skin	Look for scars, sinuses, dressings or skin changes around the hip
	For swellings	Swelling is seldom present
	For deformities	With the patient standing, note any pelvic tilt (which may mask leg shortening), and whether the spine is straight Apparent shortening of the leg can arise because of a flexion or adduction deformity True shortening is common in neck of femur fractures
	For muscle wasting	Look for quadriceps or gluteal wasting
Feel	The skin and surrounding tissues	Trochanteric bursitis, associated with numerous inflammatory arthritides, produces tenderness over the lateral thigh and pelvis
	The joint (at rest)	Usually unhelpful
Move	The joint The hip is a ball and socket joint that flexes, extends, abducts, adducts, externally and internally rotates and circumducts	 Test flexion – normal to 120°
		 Test abduction – normal to 45°
		 Test adduction – normal to 25°

Table 5.23 Examining the hip—cont'd

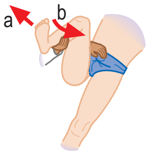
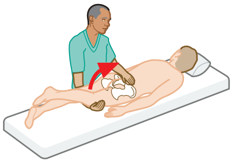
		Roll the fully extended leg and observe rotation of the foot, flex the knee and hip to 90°, then test external and internal rotation
		Roll the patient onto their back to test extension – normal to 20°

Table 5.24 Examining the knee

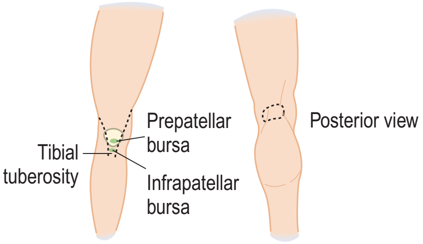
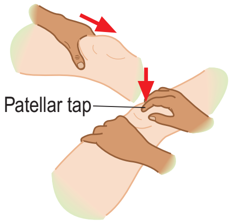
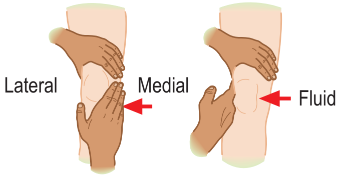
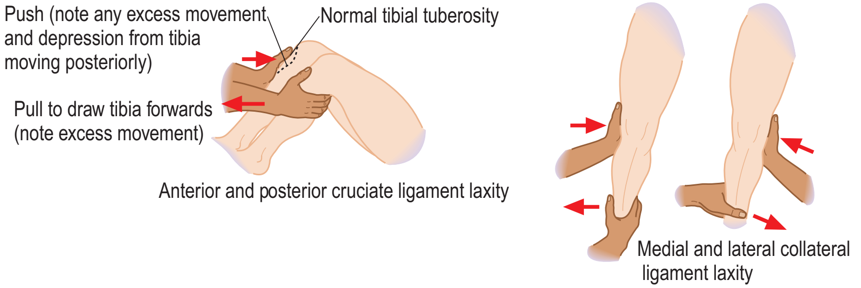
Look	At the skin	Look for scars, sinuses or erythema
	For swellings	Look for any obvious swellings or effusion including prepatellar and infrapatellar bursitis and popliteal (Baker's) cysts; if the latter ruptures, swelling may track into the calf  Prepatellar bursa Tibial tuberosity Infrapatellar bursa Posterior view Knee bursae: (a) sites of bursae; (b) popliteal cyst Look for distension of the suprapatellar pouch, reflecting a large effusion
	For deformities	Look for a valgus, varus or flexion deformity
	For muscle wasting	Look for quadriceps wasting, common with knee pathology
Feel	The skin and surrounding tissues	Feel for warmth
	The joint (at rest)	 Examining for a large knee effusion The patellar tap tests for the presence of fluid squeezed back into the joint space from the suprapatellar bursa; squeeze any excess fluid out of the suprapatellar pouch with your thumb and index finger, sliding them distally from a point some 15 cm above the knee to the upper border of the patella; with your other hand feel for the presence of a click by jerking the patella quickly downwards; the click may not be present with either a small or a tense effusion The bulge test, an addition to the patellar tap, is performed by a sudden pincing movement of the upper hand, which displaces fluid inferiorly and this fluid is palpated by a bulging apart of the fingers of the lower hand
		 Examining for a small knee effusion A smaller effusion may be detected by fluid displacement or the ripple effect; evacuate the suprapatellar pouch as for the patellar tap; the medial side of the joint is then stroked to displace any excess fluid in the main joint cavity to the lateral side of the joint; then stroking the lateral side moves the excess fluid back across the joint resulting in a visible bulge or ripple

Table 5.24 Examining the knee—cont'd

Move	The joint	Flex and extend the knees, and palpate for crepitus. Test the stability of the cruciate and collateral ligaments (although more likely to be unstable in orthopaedic settings, e.g. sports injuries)  Push (note any excess movement and depression from tibia moving posteriorly) Normal tibial tuberosity Pull to draw tibia forwards (note excess movement) Anterior and posterior cruciate ligament laxity Medial and lateral collateral ligament laxity

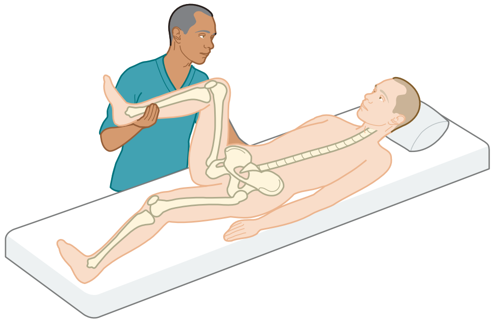


Figure 5.33 Thomas's test.

The ankles and feet

- Ask whether there is pain.
- Proceed to look, feel and move (Table 5.25).

Summary

A summary of the legs examination sequence is in the Summary box.

SUMMARY BOX – LEGS EXAMINATION SEQUENCE

For each region:
- Look at the skin
- Look for swellings
- Look for deformities
- Look for muscle wasting
- Feel the skin and surrounding tissues
- Feel the joints at rest
- Move the joints.

EXAMINATION OF THE SPINE

Neurological examination of the limbs for signs referable to the spinal cord is described on Station 3. The look, feel and move approach (Table 5.26) is also appropriate for examining the spine.

Further assessment

Nerve stretch tests for sciatic and femoral nerve impingement are an important part of spinal examination. In the *sciatic nerve stretch test* the supine patient's straight leg raising is limited by pain produced by tension of nerve roots supplying the sciatic nerve (L4–S2), commonly tensed over a prolapsed disc (commonly at vertebral level L4/5 or L5/S1). Pain may be in the back of the leg, sometimes radiating to the lumbar region. Tension is increased by dorsiflexion of the foot (which tugs the distal component of the sciatic nerve, the posterior tibial nerve) and relieved by flexion of the knee. In the *femoral nerve stretch* test the prone patient's femoral nerve roots (L2–4) are tightened by flexion of the knee, causing pain radiating into the back. The femoral roots may be further tensed by extending the hip joint, producing increasing pain.

Summary

A summary of the spine examination sequence is in the Summary box.

SUMMARY BOX – SPINE EXAMINATION SEQUENCE

For each region:
- Look at the skin
- Look for swellings
- Look for deformities
- Look for muscle wasting
- Feel the skin and surrounding tissues
- Feel the joints at rest
- Move the joints
- Consider performing nerve stretch tests.

Table 5.25 Examining the ankles and the feet

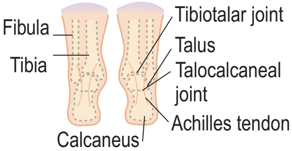
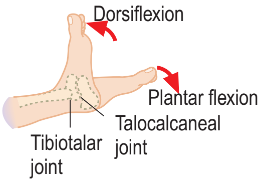
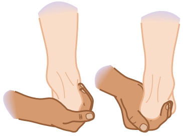
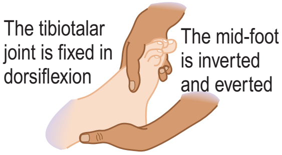
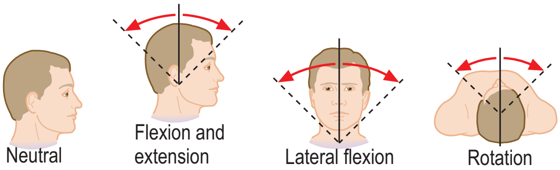
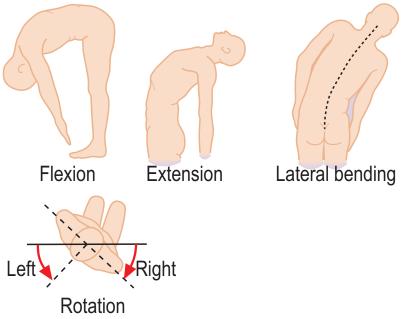
Look	At the skin	Look for erythema, scars, sinuses, nail changes or vasculitis		
	For swellings	Look for synovitis or gout		
	For deformities	Note pes planus (flat foot) or pes cavus (high arch) and any abnormal forefoot appearances such as hallux valgus, hallux rigidus or dactylitis		
	For muscle wasting	Usually reflects peripheral nerve disease		
Feel	The skin and surrounding tissues	Feel for tenderness; flexor and extensor tendonitis is common in inflammatory arthritis and overuse, plantar fasciitis is common in the spondyloarthropathies		
	The joints (at rest)	Feel for synovitis		
Move	The joints	Active	Test the active range of plantar and dorsiflexion at the ankle and inversion and eversion	
		Passive There are three main sets of joints in the ankle and foot • The hindfoot – the true ankle or tibiotalar joint (dorsiflexes by anterior tibialis and plantar flexes by gastrocnemius / soleus) and the talocalcaneal joint • The midfoot • The metatarsophalangeal and interphalangeal joints	 Fibula Tibia Calcaneus Tibiotalar joint Talus Talocalcaneal joint Achilles tendon	
			 Dorsiflexion Plantar flexion Talocalcaneal joint Tibiotalar joint	Test dorsiflexion and plantar flexion Failure of plantar flexion when patient kneels on a chair and calf is squeezed is pathognomonic of Achilles rupture
				Stabilise the hindfoot (cupping the patient's ankle in dorsiflexion) and then invert and evert
			 The tibiotalar joint is fixed in dorsiflexion The mid-foot is inverted and everted	Cup the calcaneum in your hand and test flexion / extension and inversion / eversion
				Flex and extend the toes

Table 5.26 Examining the spine

Look	At the skin	Usually no signs
	For swellings	Usually no signs
	For deformities	Look for kyphosis, marked lordosis or scoliosis Note the 'question mark' posture of ankylosing spondylitis
	For muscle wasting	
Feel	The skin and surrounding tissues	Feel the midline spinous processes and confirm alignment. Prominence, especially in the thoracic spine, may indicate anterior wedge compression of a vertebra Feel the paraspinal soft tissues for tenderness
	The joints (at rest)	Lightly percuss the spine for tenderness

Table 5.26 Examining the spine—cont'd

Move	The joints	 Neutral Flexion and extension Lateral flexion Rotation	Test flexion, extension, lateral flexion and rotation at the cervical spine
		 Flexion Extension Lateral bending Left Right Rotation	Test flexion, extension, lateral flexion and rotation at the thoracic and lumbar spine

Cases

CASE 5.11 RHEUMATOID HANDS AND RHEUMATOID ARTHRITIS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

> Re: Mrs Susan Fletcher, aged 55 years
>
> This woman has painful, swollen joints in her hand. She is being treated on your ward with an infected leg ulcer.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 55-year-old woman in hospital with an infected leg ulcer. You mention to the doctor that your hands are painful and swollen. You have a history of rheumatoid arthritis under the care of a rheumatologist previously but have not been followed up for some years. You used to take methotrexate. You also wonder if the ulcer could be related to the rheumatoid.

Focused history and examination

Initial history

- Ask about symptoms, e.g. pain, swelling.
- Ask about duration of symptoms.
- Ask about past medical history, enquiring about investigations and treatments to date.

Initial examination

- Examine the hands for signs of the *symmetrical deforming polyarthritis* (Box 5.8) of rheumatoid arthritis.
- Psoriatic arthritis may mimic rheumatoid arthritis in the hand. Look at the elbows for rheumatoid nodules (Fig. 5.36) or psoriatic plaques to help differentiate. Psoriatic arthritis commonly involves the distal interphalangeal (DIP) joints and causes nail pitting. Osteoarthritis also affects small and large joints and may be symmetrical, but Heberden's (DIP joint) and Bouchard's (proximal interphalangeal (PIP) joint) nodes are bony swellings, not soft synovial swellings.

Diagnostic criteria for rheumatoid arthritis are given in Box 5.9 for reference.

Further assessment

- Ask whether other joints are affected. Joints other than the hand affected in rheumatoid arthritis include the shoulder, elbow (flexion contractures), wrist, knee (synovial hypertrophy, ligament laxity, chronic effusion), ankle, foot (e.g. eversion at the subtalar joint, plantar subluxation of the metatarsal heads, widening of the forefoot, hallux valgus and lateral deviation/dorsal subluxation of the toes), cervical spine and temporomandibular joint. Tenosynovitis and bursitis commonly accompany joint disease, e.g. rotator cuff tendonitis, subacromial bursitis, De Quervain's tenosynovitis, hand extensor and flexor tendonitis, trochanteric bursitis.

- Consider extra-articular features of rheumatoid arthritis (Table 5.27). These affect about a third

Box 5.8 **Examination findings in rheumatoid hands**

Skin

There may be *palmar erythema*. *Cutaneous vasculitis* appears as crops of small brown spots at the nail folds, and as digital pulp infarcts.

Swellings

There may be marked soft-tissue swelling of the *metacarpophalangeal (MCP) joints and wrists*. The *proximal interphalangeal (PIP) joints* may be swollen (the interphalangeal joint of the thumb behaves as a PIP joint). The distal interphalangeal (DIP) joints are spared. There may be active synovitis with fusiform spongy swelling of joints.

Soft-tissue swelling around a joint is the hallmark of inflammatory joint disease and associated stiffness is worse after inactivity and relieved by movement. Pain, stiffness (early morning lasting > 30 minutes) and warmth are the other features of synovial inflammation, but erythema is rare. Pain originates predominantly from the joint capsule, abundantly supplied with pain fibres.

Deformities

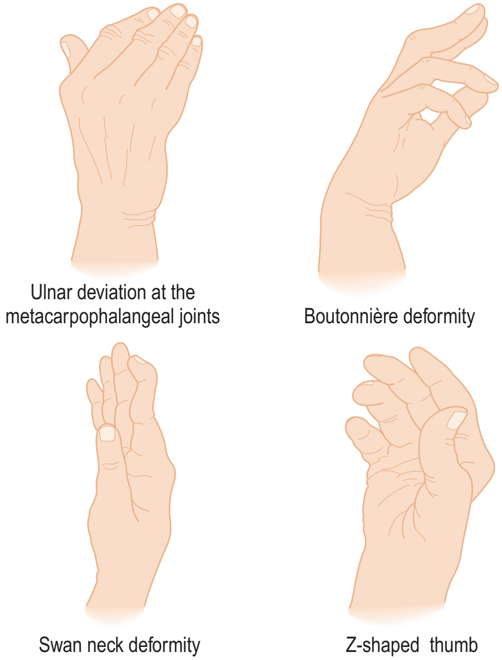
There may be:

- *Ulnar deviation* of the fingers due to subluxation or dislocation at the MCP joints (ulnar deviation also results from displaced extensor tendons)
- *Swan neck deformities* of the fingers (flexion deformity of the DIP joint, with a hyperextended PIP joint)
- *Boutonnière deformities* of the fingers (extended DIP joint caused by rupture of the extensor tendon slip, with a flexed PIP joint)
- *Z-shaped thumbs* (flexed MCP joint, with extended IP joint).

These deformities are shown in Figures 5.34 and 5.35.

Muscle wasting

This is usually generalised, predominantly from disuse. There is thenar and hypothenar wasting (compare with isolated median or ulnar neuropathies); interosseous wasting is very common.



Ulnar deviation at the metacarpophalangeal joints

Boutonnière deformity

Swan neck deformity

Z-shaped thumb

Figure 5.34 Finger deformities in rheumatoid arthritis.

Box 5.9 **Diagnostic criteria for rheumatoid arthritis (RA) (American College of Rheumatology)**

RA is a chronic inflammatory, symmetrical, predominantly small joint, polyarthritis. It is an autoimmune disease, mediated by pro-inflammatory cytokines. There is a strong HLA DR4 association. It affects around 1% of people and its onset is commonly in the fifth decade. Diagnostic criteria are:

- Morning stiffness > 1 hour*
- Arthritis of three or more joint areas – proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, metatarsophalangeal*
- Arthritis of hand joints*
- Symmetrical arthritis
- Rheumatoid nodules
- Rheumatoid factor positivity
- Radiological features (e.g. joint erosions).

Four criteria are required (* must be present for at least 6 weeks). The usual pattern is insidious, over weeks to months, starting with fatigue, anorexia and vague musculoskeletal symptoms. Less frequently it appears over a week or two, and rarely over a few days. A palindrome refers to episodic features with complete resolution in between, such as acute, self-limiting swelling of a knee. Extra-articular onset is recognised.

The Guideline Development Group (GDG) for the National Institute for Health and Clinical Excellence accepts a clinical diagnosis of RA as being more important than the 1987 American Rheumatism Association (which would become the American College of Rheumatology) classification criteria because an early persistent synovitis in which other pathologies have been ruled out needs to be treated as if it is RA to try to prevent damage to joints. International committees are addressing the diagnostic criteria for early RA. The GDG categorises RA into two categories: 'recent onset' (disease duration of up to 2 years) and 'established' (disease duration of longer than 2 years).

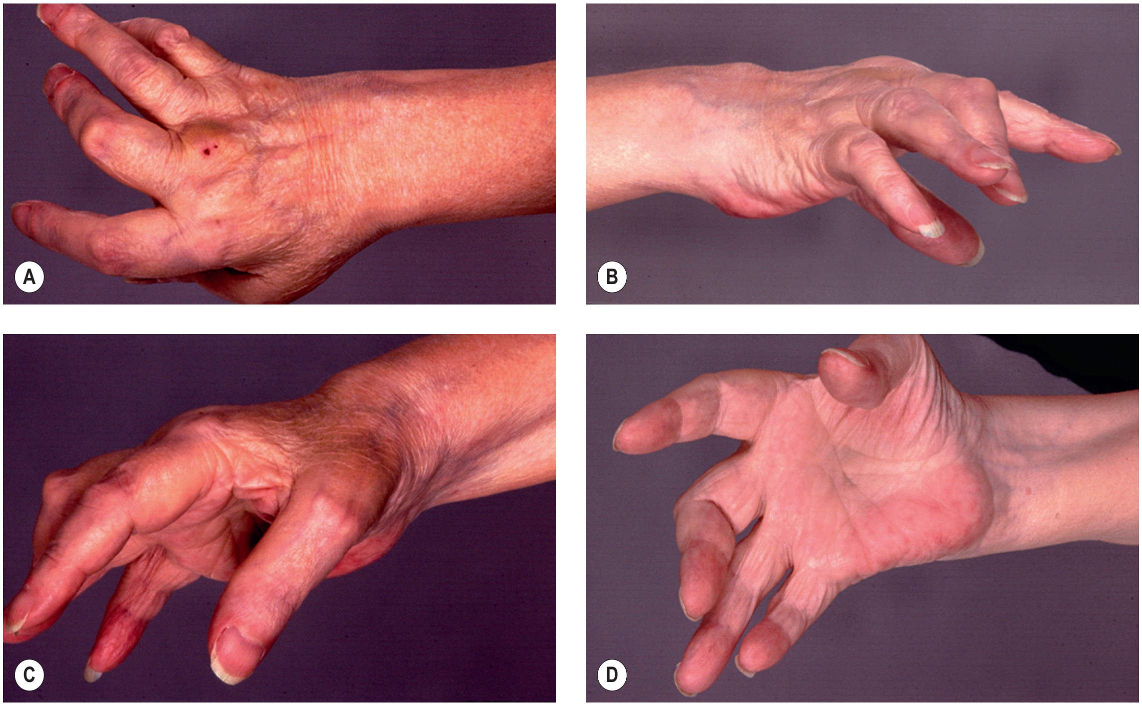


Figure 5.35 (A–D) Finger deformities in rheumatoid arthritis.

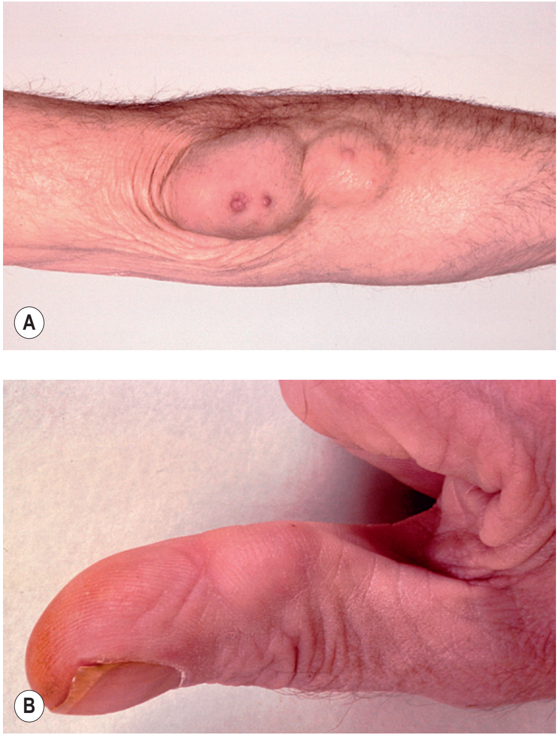


Figure 5.36 Rheumatoid nodules: (A) elbow, (B) thumb.

of patients and are generally associated with rheumatoid factor positivity. Asks if she is aware of any symptoms other than in the hands.

- Explore concerns and function. Function can be assessed by a simple screen of pincer, grip and arm movements and by asking about routine activities such as fastening buttons, using keys, writing, taking coins out of pockets, holding cups, opening jars, cleaning teeth, combing hair, getting dressed and reaching into kitchen cupboards. Specific ways of assessing disease activity include health assessment questionnaires, pain assessments, tender joint scores, swollen joint scores, duration of morning stiffness and monitoring of inflammatory markers. Numerous factors influence prognosis in rheumatoid arthritis (Box 5.10).

Feedback to patient

This is almost certainly a flare-up of the rheumatoid arthritis. It would be sensible for me to discuss treatment with a rheumatologist. It may be that something other than the methotrexate will be needed in the short term to settle things down such as steroids. It may also be worth your rheumatologist discussing other disease-modifying drugs with you. Methotrexate can of course suppress the immune system and make infection more likely, such as with the infected ulcer, although it may be a balance of risk as most disease-modifying drugs for rheumatoid

Table 5.27 Extra-articular features of rheumatoid disease

System or feature	Possible manifestations	Comment
Cardiovascular	Accelerated cardiovascular disease Constrictive pericarditis Pericardial effusion Mitral regurgitation	Severe RA carries a 5-year survival rate similar to three-vessel coronary artery disease. Although increased mortality has been linked with disease severity, disability and extra-articular disease, accelerated atherosclerosis remains the main culprit. Traditional risk factors are partly to blame, but chronic inflammation and endothelial damage associated with rheumatoid disease are important contributors that may enhance traditional factors, such as the association between systemic inflammation and arterial wall stiffness in hypertension, or the pro-atherogenic lipid profile (high LDL and lipoprotein(a), low HDL) seen with rheumatoid disease activity. Patients with RA have a higher incidence of diastolic hypertension, angina and stroke, and subclinical vascular disease such as shown by a higher prevalence of carotid disease, peripheral arterial disease and electrographic abnormalities. Deaths from CVD occur earlier than in the general population. There are many reasons why CVD is increased in RA: • Oxidised LDL (oxLDL) and antibodies to oxLDL are present at higher levels in active disease. OxLDL is abundant in atherosclerotic lesions, and prolongs the inflammatory response by altering apoptotic cell clearance. OxLDL is produced in the inflamed rheumatoid joint, where it similarly prolongs inflammation • CRP is raised in acute coronary syndromes, involved in initiation and progression of atherosclerotic lesions, and independently predicts the risk of future myocardial infarction, stroke and death. Higher levels of CRP are associated with CVD in non-RA patients, and treatment of CVD with statins or angiotensin-converting enzyme inhibitors can lower CRP levels. Rather than simply a marker of systemic inflammation, CRP has direct pro-inflammatory effects at many sites, e.g. it activates vascular endothelial cells to express adhesion molecules • Elevated homocysteine levels are associated with CVD and present in higher concentrations in RA joints. Homocysteine is probably an epiphenomenon rather than cause of CVD • RA causes physical deconditioning as a result of disability, often with obesity
Lung (findings more common at autopsy than clinically)	Pleuritic pain Pleural effusions Interstitial lung disease Pulmonary nodules	Methotrexate also causes fibrosis and nodules In Caplan's syndrome, massive fibrotic nodules coexist with coal dust exposure
Neurological	Entrapment neuropathies (carpal tunnel syndrome, foot and wrist drops)	Entrapment by synovial swelling
	Cervical myeloradiculopathy	Subluxation of the atlantoaxial joint occasionally occurs owing to laxity of the transverse ligament of the atlas (synovitis of facet joints may also contribute to instability); subluxation is shown by flexion and extension radiographs demonstrating increased distance between the posterior aspect of the C1 vertebral body and the anterior aspect of the odontoid process of C2
	Dysphonia (rare) Hearing loss (rare) Sensory polyneuropathy	Cricoarytenoid arthritis Synovial involvement of ossicles Caused by mononeuritis multiplex
Vasculitis (small vessel)	Usually restricted to skin, e.g. nail folds Digital gangrene Cutaneous ulceration including pyoderma gangrenosum Peripheral neuropathy Mononeuritis multiplex Coronary, renal, cerebral or mesenteric vasculitis (all very rare) Raynaud's phenomenon	Rheumatoid factor highly positive
Rheumatoid nodules (soft-tissue nodules, not to be confused with tendon xanthomata)	Sites: Extensor tendons of hand Trigger finger (thickening, usually without nodules, of flexor aspect) Pressure points, e.g. elbows, Achilles tendons, bridge of nose if spectacles Lungs Pericardium Sclera (rare)	Rheumatoid factor invariably positive

Table 5.27 Extra-articular features of rheumatoid disease—cont'd

System or feature	Possible manifestations	Comment
Eye	Episcleritis Scleritis Keratoconjunctivitis sicca (40%)	Recurrent scleritis may progress to scleromalacia perforans

Sjögren's syndrome

This is a chronic inflammatory, lymphoproliferative disease with autoimmune exocrinopathy:

- Primary Sjögren's syndrome is defined by xerostomia (dry mouth caused by decreased salivary gland secretion) and xerophthalmitis (dry eye, also known as keratoconjunctivitis sicca, caused by decreased lacrimal secretion) without other autoimmune disease.
- Secondary Sjögren's syndrome occurs with RA, SLE or other autoimmune connective tissue disease.

Sjögren's syndrome is the second commonest autoimmune rheumatic disease after RA and may affect up to 3–4% of the adult population with a female–male ratio of 9 : 1. Genetic predisposition includes *HLA DR3* and *DR52* and *DQ*. Environmental agents include herpes viruses, cytomegalovirus and Epstein–Barr virus. Between 5% and 10% of patients develop non-Hodgkin's B-cell lymphoma.

	Manifestation	Symptoms and signs	Diagnosis
Glandular	Ocular	Dry mouth – xerostomia Lack of saliva pool floor of mouth Swelling of salivary glands Dysphagia	European diagnostic criteria require at least four of six items: • Ocular symptoms • Oral symptoms • Evidence of xerophthalmitis (Schirmer's test or rose bengal staining); Schirmer's test uses standardised test strips placed between the eyeball and the lateral part of the inferior lid, positive if < 5 mm of wetness at 5 minutes • Focal sialadenitis from minor salivary gland involvement (lip biopsy) • Instrumental evidence of salivary gland involvement (salivary flow rate – clinical setting, parotid sialography) • Autoantibodies present (anti-Ro or anti-La) Positive antibodies or a positive lip biopsy should be mandatory for diagnosis
	Oral	Dry, gritty eyes – xerophthalmitis Scleritis Inflammatory nodules Sterile corneal ulcers	
Systemic Many manifestations caused by vasculitis or tissue lymphoid infiltration	Joint involvement	Symmetrical, small joint arthralgia with mild synovitis	
	Vasculitis of small- or medium-sized vessels	Purpuric rash Skin ulceration Urticaria Neuropathy	
	Gastrointestinal Primary biliary cirrhosis or autoimmune hepatitis may be associated	Dysphagia (dry pharynx or oesophageal dysmotility)	
	Pulmonary	Chronic bronchitis Mucus plugging Lymphocytic interstitial pneumonitis Pleural effusions Pulmonary hypertension	
	Renal Tubular dysfunction and renal tubular acidosis	Renal calculi Nephrocalcinosis Hypokalaemic muscle weakness	
	Neurological	Peripheral neuropathy Mononeuropathy	

Table 5.27 Extra-articular features of rheumatoid disease—cont'd

System or feature	Possible manifestations	Comment
Skin	Palmar erythema Livedo reticularis Pyoderma gangrenosum	
Felty's syndrome	Rheumatoid arthritis + Splenomegaly + Leucopenia	Hypersplenism not invariable Severe neutropenia (even thrombocytopenia and anaemia) may occur without hypersplenism
Kidney	Nephrotic syndrome	Caused by amyloid deposition
Systemic features	Malaise Weight loss Lymphadenopathy Amyloid accumulation Anaemia	Not specific to rheumatoid arthritis; caused by pro-inflammatory immune response Causes of anaemia in rheumatoid arthritis include: • Anaemia of chronic disease • Non-steroidal anti-inflammatory drug-related gastritis/peptic ulceration • Bone marrow suppression from disease-modifying anti-rheumatic drugs • Splenomegaly in Felty's syndrome • Megaloblastic anaemia (associated pernicious anaemia or methotrexate-related folate deficiency)

CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Box 5.10 **Factors associated with a less favourable prognosis in rheumatoid arthritis**

- High-titre rheumatoid factor positivity (70% of patients)
- Many active joints at presentation
- Extra-articular disease (e.g. nodules, vasculitis)
- Severe disability at presentation
- Joint erosions/deformity early in disease
- High erythrocyte sedimentation rate or C-reactive protein at presentation
- HLA DR4 presence, especially homozygosity
- Family history

will do this to an extent. The other consideration I think is whether or not the ulcer could be related to the rheumatoid arthritis, which can sometimes be the case. We will aim to get these answers quickly, and of course do all we can to relieve the pain and other symptoms quickly. Are there any questions you have?

Feedback to examiners

Summarise the key history and examination findings

This woman has soft-tissue swelling of the metacarpophalangeal joints and proximal interphalangeal joints with evidence of active synovitis. She has typical hand deformities of rheumatoid arthritis including ulnar deviation, swan neck and Boutonnière deformities and Z-thumbs.

Provide a diagnosis or differential diagnosis with supporting evidence

Given her past medical history rheumatoid arthritis seems likely, and whilst psoriatic arthropathy can occasionally produce similar changes the presence of nodules further supports rheumatoid arthritis as well as providing prognostic information.

Outline an investigation and management plan

Investigations in rheumatoid arthritis [Box 5.11] may include blood testing for rheumatoid factor or anti-cyclic citrullinated peptide, synovial fluid analysis and radiology, but these may not be necessary here. Treatment goals in rheumatoid arthritis are pain relief, reduction of inflammation, limitation of joint damage, control of systemic disease and maintenance of function. No treatment is curative. Analgesics, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors help pain but do not control inflammation. Potential side effects are peptic ulceration, interstitial nephritis, fluid retention and worsening of asthma with non-steroidal antiinflammatory drugs and cyclo-oxygenase-2 inhibitors; a proton pump inhibitor should be considered with these drugs and these drugs should be avoided if already on aspirin. Disease-modifying anti-rheumatic drugs including methotrexate and sulfasalazine and biological agents have a place early in disease to limit progression [Box 5.12]. Short-term systemic, intramuscular or intra-articular glucocorticoids are used for symptom relief. They attenuate the acute-phase response but do not appear to modify disease and use must be carefully balanced against side effects. Physiotherapists, occupational therapists, podiatrists and surgeons may have important roles.

Box 5.11 **Investigations in rheumatoid arthritis**

Rheumatoid factor (RF)

RFs are antibodies against the Fc portion of immunoglobulin G. They may be of any isotype but only immunoglobulin M was traditionally detected by the now superseded latex agglutination test. An easy way to consider RF is to first consider that antibodies directed against other antibodies is a normal phenomenon. New antibodies are created continuously in response to an infinite variety of antigens in the environment; some antibodies, when newly formed, may also be seen by the immune system as foreign and 'anti-antibodies' are produced against them. Sometimes a cascade of antibody against antibody may be triggered. Some of the anti-antibodies produced in this way are RFs and, hence, RFs are not specific to rheumatoid arthritis. They may be detected transiently after many acute infections, may be present in low titres in chronic infections, and are sometimes found in chronic inflammatory disorders such as systemic lupus erythematosus and scleroderma. RFs are detectable in 5% of the normal population and in up to 25% of elderly people – simply because elderly people have been exposed for a longer time to the environmental stimuli that engender such antibodies. Up to 70% of patients with rheumatoid arthritis are RF positive.

Anti-cyclic citrullinated peptide (anti-CPP)

Anti-CPP antibodies are detected in many RF-negative patients, a more sensitive test than RF itself. Anti-CPP antibodies occur in 80% of patients with established rheumatoid arthritis and have a specificity of 95% and a sensitivity of around 65%. Like RF, they also seem to predict development of erosive rheumatoid arthritis.

Synovial fluid

Fluid is often turbid, with low viscosity, high protein concentration, low or normal glucose concentration, low complement levels and an elevated white cell count (5–50 000 cells / ml). There is seldom a place for synovial fluid examination other than to exclude infection.

Some radiological features of rheumatoid arthritis

X-rays of the hands and feet early in the course of the disease in people with persistent synovitis in these joints is important. Features include:

- Soft-tissue swelling together with juxta-articular osteoporosis in early disease
- Joint space narrowing
- Joint erosions
- Cyst formation
- Joint destruction
- Subluxation / dislocation.

Monitoring

- C-reactive protein and key components of disease activity (using a composite score such as DAS28) should be measured regularly in people with rheumatoid arthritis to inform decision making about increasing treatment to control disease, cautiously decreasing treatment when disease is controlled.

Box 5.12 **Drugs in rheumatoid arthritis**

Disease-modifying anti-rheumatic drugs (DMARDs)

DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, gold, ciclosporin, leflunomide) delay disease progression and reduce subsequent disability, and should be introduced early in disease. All agents are of similar efficacy at optimum dosage except for hydroxychloroquine and auranofin, which appear slightly less effective. Many DMARDs can cause bone marrow suppression and skin rashes. Gold and penicillamine may cause nephrotic syndrome. Penicillamine is associated with drug-induced lupus and autoimmune disease. Methotrexate and sulfasalazine are most widely used but monotherapy with any agent wanes in effect with time. Combinations are therefore used to sustain benefit:

- In newly diagnosed active RA, methrotrexate and at least one other DMARD (plus short-term glucocorticoids) are used, ideally within 3 months of the onset of persistent symptoms. Monotherapy is considered where comorbidities or pregnancy make it safer.
- In the first 2 years, provided satisfactory and sustained control, step-down combination therapy may be considered cautiously, although it may not maintain long-term benefit. After 2 years, if stable, drugs and doses may be cautiously withdrawn, but with prompt return of drugs if there are flare-ups.

Glucocorticoids

- Short-term treatment with glucocorticoids helps manage flares in people with recent-onset or established disease by rapidly decreasing inflammation.

Biological agents

Rationale

- Rheumatoid synovitis contains predominantly T lymphocytes ($CD4^+$ T-helper type 1), macrophages and fibroblasts with secretion of pro-inflammatory cytokines [interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF)-α] and metalloproteinases, which mediate tissue damage. TNF-α mediates proliferative and inflammatory aspects, and IL-1 mediates cartilage destruction and bone erosion. IL-6 mediates many actions of TNF-α and IL-1 but also recruits B cells. Most T-helper type 1 cells are memory cells but some mediate B-cell help, enhancing local auto-antibody formation. Plasma cells secreting rheumatoid factor are also present.

Agents

- Three monoclonal antibody antagonists to TNF-α are available: adalimumab (a fully humanised monoclonal antibody), etanercept (a recombinant TNF receptor immunoglobulin G

Box 5.12 **Drugs in rheumatoid arthritis—cont'd**

fusion protein) and infliximab (a chimeric immunoglobulin G antibody).

- Rituximab, a B-cell-targeted treatment acting on CD20, is considered for patients with severe active rheumatoid arthritis failing to respond to DMARDs and TNF-α modification therapy.
- Abatacept inhibits the co-stimulatory signal for T-cell activation.
- Risks are outlined in Case 2.46.

TNF-α inhibitors

- The TNF-α inhibitors are recommended for patients with active rheumatoid arthritis as measured by a disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart, who have tried two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as 6 months, with 2 months at standard dose, unless toxicity has limited the dose or duration of treatment.
- TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or methotrexate is inappropriate, adalimumab and etanercept may be used as monotherapy.
- Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy, defined as improvement in DAS28 of 1.2 points or more. After initial response, treatment should be monitored no less frequently than 6-monthly with assessment of DAS28 and withdrawn if an adequate response is not maintained. Treatment should normally be initiated with the least expensive drug.
- Use of the TNF-α inhibitors in severe, active and progressive rheumatoid arthritis not previously treated with methotrexate or other DMARDs is not recommended although there is some evidence to suggest that, if introduced early in disease, a significant proportion of people go into early and sustained remission which can be maintained by conventional DMARDs alone

Failure of anti-TNF-α inhibitors

- An alternative TNF-α inhibitor may be considered if treatment is withdrawn owing to an adverse event before the initial 6-month assessment of efficacy. If the first TNF-α inhibitor fails because of lack of efficacy, people may try rituximab or go back to conventional DMARDs, but there is good evidence that biologicals, including a second TNF-α inhibitor, are effective under these circumstances.
- Rituximab in combination with methotrexate is recommended for severe active rheumatoid arthritis with an inadequate response to, or where there is intolerance of, other DMARDs, including at least one TNF-α inhibitor. If rituximab is contraindicated or withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended. If rituximab cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, adalimumab and etanercept, each as monotherapy, are recommended.

CASE 5.12 ANKYLOSING SPONDYLITIS AND SPONDYLOARTHROPATHIES

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Anthony Hoskins, aged 40 years

This man is on your ward with a flare-up of ulcerative colitis, but mentions a painful spine.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 40-year-old man on the ward with a flare-up of ulcerative colitis and mention to the doctor that you have a painful neck and buttocks. You attributed it to 'wear and tear' previously as you have worked as a builder for many years and carried heavy loads. Your pain is worse in the morning after a period of rest. Your upper spine, particularly, has become curved. You are self-employed and now worried that work is becoming more difficult, even getting in and out of trucks.

Focused history and examination

Initial history

- Ask about stiffness of the lumbar or dorsal spine, and those features of back pain listed in Box 5.13. The back pain of spondyloarthropathies, unlike mechanical back pain, has typical features.
- Ask about alternating buttock pain.

- Ask about a past history of psoriasis and inflammatory bowel disease.
- Ask about a family history of similar problems.

All of the above symptoms are common to ankylosing spondylitis (the primary spondyloarthropathy) and the other spondyloarthropathies. There is considerable overlap of features between the spondyloarthropathies (Box 5.14).

Some differentiating articular signs of spondyloarthropathies from rheumatoid arthritis and osteoarthritis are shown in Table 5.28.

Initial examination

- There may be *kyphosis* with a characteristic *question mark* posture (Fig. 5.37).
- There may be *restriction of spinal movement in all directions* (extension, lateral flexion, rotation) and there would be a *positive modified Schober's test* (marking the level of the posterior iliac spines and sacral dimples, and a point 10 cm above this in the midline, when the patient flexes forward the distance between the two points normally increases to at least 15 cm but does not in a positive test). Upper spine involvement is demonstrated by the *wall–occiput* test (Fig. 5.38).

Further assessment

- Some 'A's are associated with ankylosing spondylitis (Box 5.15). Ask about heel pain, eye problems, heart valve problems and lung problems.
- Ask about skin symptoms (psoriasis), recent infection (reactive arthritis) and bowel symptoms (enteropathic arthritis, associated with inflammatory bowel disease). The seronegative spondyloarthropathies (Box 5.16) lack rheumatoid factor positivity and are associated with human leucocyte antigen (HLA) B27. A family history is common. HLA B27 is positive in 5–10% of the white population and in 90% of patients with ankylosing

Box 5.13 **Typical features of spondyloarthropathy back pain**

- Worse sitting, lying and resting
- Worse with prolonged immobility
- Improved by exercise
- Associated with prolonged (at least 1 hour) morning stiffness.

These symptoms also tend to be true for joint symptoms in any inflammatory arthritis.

Box 5.14 **Musculoskeletal features of ankylosing spondylitis and the spondyloarthropathies**

Spondylitis (inflammatory spine disease)

This is characterised by insidious onset, persistence for > 3 months, morning stiffness and improvement with exercise. Enthesitis contributes to spondylitis because destruction of the insertion sites of vertebral discs to vertebrae leads to squaring of the vertebrae. Syndesmophytes (because of reactive bone formation) sometimes link vertebrae. Calcification within the anterior and posterior spinal ligaments gives rise to the characteristic but rare bamboo (not a panda in sight) spine.

Sacroiliitis (the main diagnostic feature)

This often causes alternating buttock pain, especially at night. Sacroiliitis tends to be symmetrical in ankylosing spondylitis but asymmetrical or unilateral in the other spondyloarthropathies. Severity is graded radiographically by the extent of joint distortion.

Enthesitis (the main pathological feature)

Many symptoms in spondyloarthropathies are the result of enthesitis, which refers to inflammation (+/− fibrosis, calcification and ossification) at the insertion site (enthesis) of a tendon, ligament or joint capsule to bone. Heel pain, worse when starting to walk in the morning and associated with a 'burning sole', is the result of plantar fasciitis and is the commonest enthesopathy. Other sites include the insertion of the Achilles tendon to the calcaneus (Achilles tendonitis), the capsular insertions of the costovertebral, sternoclavicular, manubriosternal and costochondral junctions, the capsules and ligaments around finger joints, and finger tendon sheaths.

Peripheral large joint monoarthritis or oligoarthritis

This tends to be asymmetrical and to affect the lower limbs (hip, knee or ankle). It may predate or follow spine disease by several years.

Dactylitis

This refers to the sausage swelling of a digit resulting from joint and tendon / tendon sheath swelling.

Table 5.28 Articular signs differentiating a spondyloarthropathy from rheumatoid arthritis and osteoarthritis

	Spondyloarthropathy	Rheumatoid arthritis	Osteoarthritis
Symmetry	Asymmetrical	Symmetrical	Asymmetrical / symmetrical
Joints affected	Peripheral arthritis affecting mostly large joints, e.g. knees, hips, ankles	Peripheral arthritis affecting mostly small joints, e.g. metacarpophalangeal joints, wrists	Small and large joints affected, e.g. hips, first carpometacarpal joint, knees, hips
Spinal involvement	Spondylitis Sacroiliitis	Atlanto-axial subluxation	Lumbar and cervical degeneration

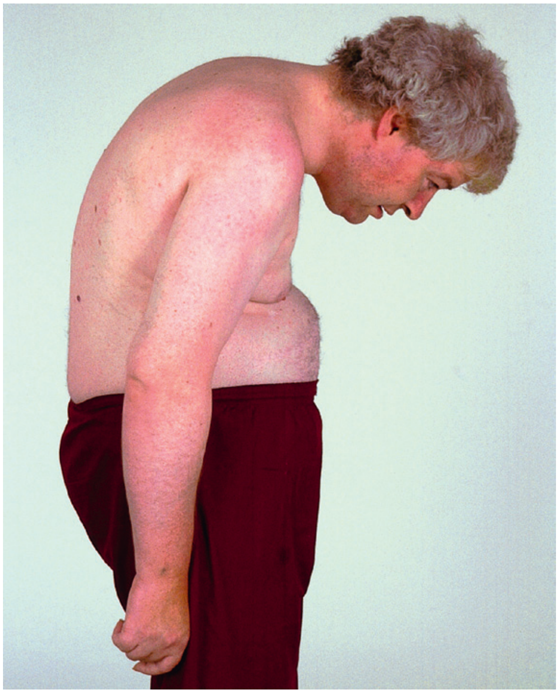


Figure 5.37 Ankylosing spondylitis.

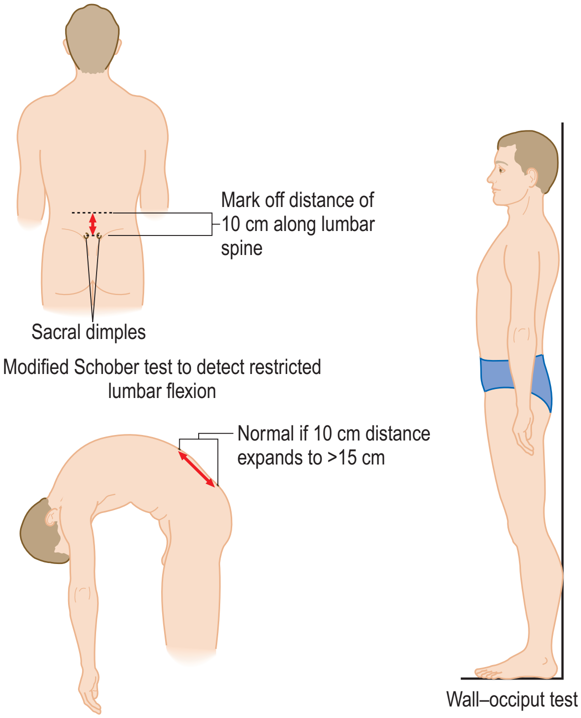


Figure 5.38 Modified Schober's test and wall–occiput test.

Box 5.15 **'A's associated with ankylosing spondylitis**

- **A**chilles tendonitis and plantar fasciitis
- **A**nterior uveitis
- **A**ortic regurgitation and aortitis
- **A**pical lung fibrosis
- **A**trioventricular heart block
- **A**myloidosis

Box 5.16 **The seronegative spondyloarthopathies**

Ankylosing spondylitis

Ankylosing spondylitis is the primary spondyloarthropathy affecting 0.2–0.5% of the population with symmetrical pain and absence of features to suggest one of the other conditions. Age of onset is 15–40 years and the male–female ratio is around 3 : 1. The modified New York criteria for diagnosis require the presence of at least one clinical criterion plus one radiological criterion:

- Low back pain of at least 3 months' duration, with inflammatory characteristics
- Limitation of lumbar spine mobility in both sagittal and frontal planes
- Limitation of chest expansion relative to normal age- and sex-matched values
- Unilateral sacroiliitis (grades 3–4) or bilateral sacroiliitis (grade 2)

  (grade 0 – normal; grade 1 – suspicious changes; grade 2 – minimal sacroiliitis; grade 3 – moderate sacroiliitis; grade 4 – ankylosis).

Criteria for early diagnosis, based on the co-occurrence of inflammatory spinal pain and demonstration of sacroiliitis by magnetic resonance scanning, are emerging.

Psoriatic arthritis

Psoriatic arthropathy (Fig. 5.39) affects up to 10% of patients with psoriasis (Fig. 5.40) and may precede or follow skin disease by months or even years. There are, in theory, five types of arthropathy (Case 5.1); radiologically, there may be erosions and severe joint destruction.

Reactive arthritis (including Reiter's syndrome)

Reactive arthritis refers to arthritis after any infection. It may affect small or large peripheral joints, with features of a spondyloarthropathy. Reiter's syndrome, a form of reactive arthritis, often follows urethritis / cervicitis (e.g. *Chlamydia*) or dysenteric infections (e.g. *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* spp.). The classic triad is arthritis, urethritis and conjunctivitis / anterior uveitis. The classic triad is not always complete, and common additional findings include mouth ulceration, circinate balanitis, persistent plantar fasciitis and keratoderma blennorrhagica (hyperkeratotic vesicles, often on soles or palms).

Enteropathic arthritis

Associated with inflammatory bowel disease.

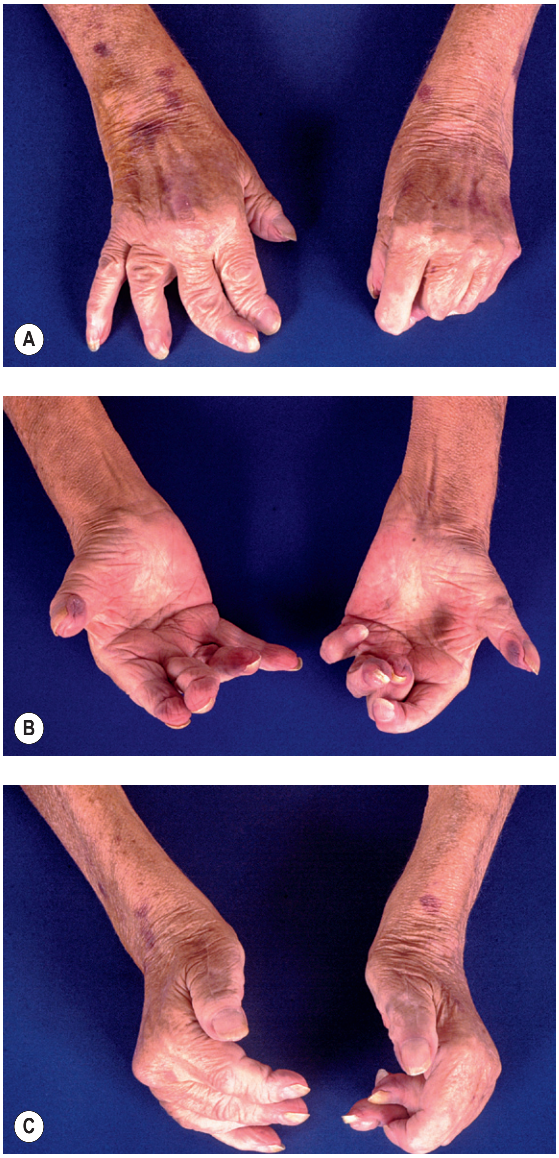


Figure 5.39 (A–C) Psoriatic arthropathy.

spondylitis, 70% with Reiter's syndrome and up to 50% with other spondyloarthropathies. The interleukin-23 receptor may also play a role. Serology is not used widely in diagnosis, which should rely on clinical and radiological assessment. Overlap of features may occur between spondyloarthropathies, e.g. a patient with psoriatic arthritis may develop anterior uveitis.

- Vertebral osteoporosis is not uncommon, and cardiovascular disease and renal impairment may complicate severe ankylosing spondylitis.
- Consider his concerns about work.

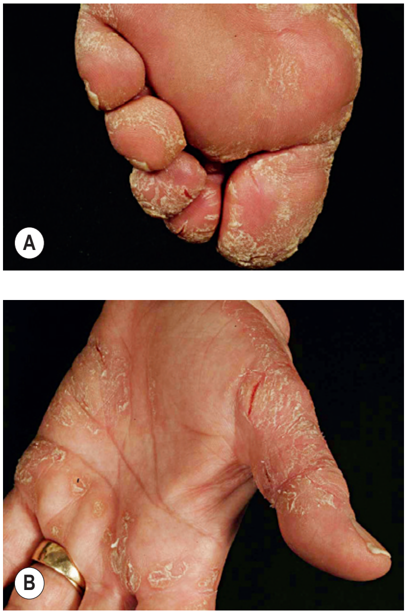


Figure 5.40 (A, B) Psoriasis.

Feedback to patient

I think this may be a condition known as ankylosing spondylitis, in which inflammation in the spine sometimes causes fusion of the vertebrae. The pain and other symptoms that you describe are very typical of this. It might be wise to obtain some X-rays of the spine and pelvis to look for any features of this condition, and if so then to discuss things with a rheumatologist who could advise on the best longer term treatment. If this is ankylosing spondylitis then the pain should respond to anti-inflammatories, which we can start now, but it will also be important to consider longer term treatments to tackle the condition itself, and there is a wide range of effective options which the rheumatologist could discuss with you. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man describes features of an inflammatory arthropathy with symptoms of spondylitis and sacroiliitis.

Provide a diagnosis or differential diagnosis with supporting evidence

He could well have ankylosing spondylitis – there does not appear to be any evidence of psoriasis or recent infection but he has inflammatory bowel disease – although overlap features of the various spondyloarthropathies is common.

Outline an investigation and management plan

Diagnosis of ankylosing spondylitis is based on clinical and radiological evidence. The radiological features of established spondylitis and sacroiliitis are useful but in acute disease X-rays are normal; symptomatic sacroiliitis can precede radiological changes by years and magnetic resonance imaging of the sacroiliac joints is increasingly used to detect early disease. Inflammatory markers are often elevated in active disease.

A dramatic improvement with non-steroidal anti-inflammatory drugs is typical in early disease. Good posture, physiotherapy and home exercises including extension exercises are important. Disease-modifying anti-rheumatic drugs similar to those used in rheumatoid arthritis may help large joint arthritis, but seem to have less effect on axial (spine disease.

Ankylosing spondylitis persists through life and fatigue may be a major symptom that is difficult to treat. Furthermore, there is no evidence that non-steroidal anti-inflammatory drugs or physiotherapy alter progression. Evidence for the benefit of 'biologics' is mostly with ankylosing spondylitis but also for psoriatic arthritis, prompting guidelines by the Assessment in Ankylosing Spondylitis Working Group and the British Society of Rheumatology. Tumour necrosis factor-α mRNA has been identified in inflamed sacroiliac joints in patients with ankylosing spondylitis and joints of patients with psoriatic arthropathy. As with rheumatoid arthritis, adalimumab, etanercept and infliximab may have roles in seronegative arthropathy, especially for axial disease. The National Institute for Health and Clinical Excellence recommends adalimumab or etanercept in severe ankylosing spondylitis with active spinal disease assessed on two separate occasions 12 weeks apart, and failure of at least two non-steroidal anti-inflammatory drugs. Infliximab is not recommended for people with ankylosing spondylitis.

Etanercept, infliximab and adalimumab are all recommended for the treatment of active and progressive psoriatic arthritis, based on specific criteria and monitoring of the Psoriatic Arthritis Response Criteria and the Psoriasis Area and Severity Index.

CASE 5.13 SYSTEMIC LUPUS ERYTHEMATOSUS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Lorna Fieldhouse, aged 29 years

This young woman has been admitted to hospital with an episode of pericarditis. Prior to this she was under investigation for a facial rash and joint symptoms.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 29-year-old woman in hospital with chest pain and a subsequent diagnosis of pericarditis. Recently you have been seen in the medical outpatient clinic with a facial rash and joint pains, with a provisional diagnosis of systemic lupus erythematosus (SLE). Your test results and follow-up with respect to this are awaited. Furthermore, you wish to become pregnant in the near future and wonder about the implications of your diagnosis.

Focused history and examination

Initial history

- Ask about current symptoms, and if she is feeling better from the symptoms of pericarditis.
- Ask about her SLE symptoms and what she has been told so far about the SLE diagnosis.
- Take a drug history – drug-induced lupus (e.g. minocycline, hydralazine, procainamide, penicillamine) is more common in males, tends to spare the nervous system and kidneys, resolves on stopping the drug and is anti-double-stranded DNA negative but histone positive.

Initial examination

- Look for the raised or *flat patches of malar erythema ('butterfly rash'), sparing the nasolabial folds* (Fig. 5.41) that are typical of the rash in SLE. The widely recognised presentation of a young woman with both a butterfly rash and inflammatory arthritis is only part of the spectrum of disease. Non-specific symptoms such as fatigue, photosensitive skin rashes, mild hair loss, Raynaud's phenomenon, oral ulcers, dry eyes and mouth, arthralgia or pleuritic chest pain are equally likely presentations.

Further assessment

SLE is a diverse autoimmune disease principally affecting women during childbearing years. The female-to-male ratio is 9 : 1. Although almost all patients have skin and

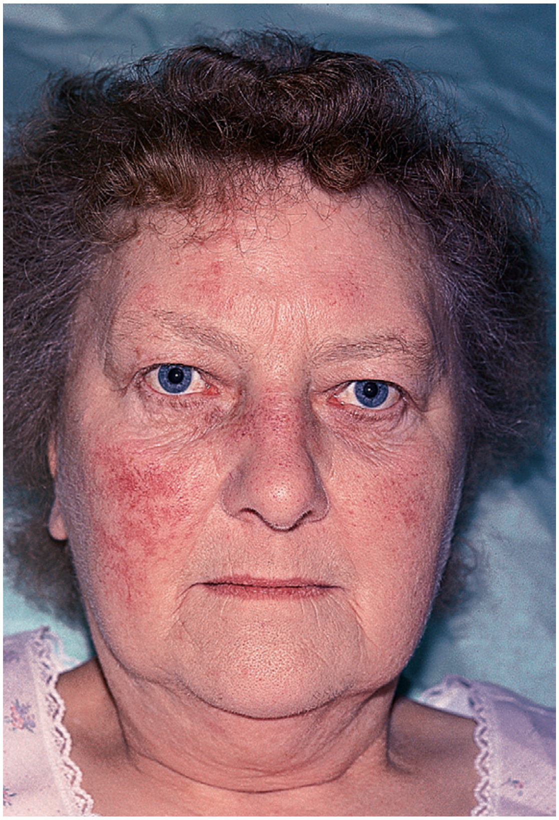


Figure 5.41 Malar rash typical of systemic lupus erythematosus.

joint disease, between 30% and 50% will develop renal, lung, heart or central nervous system involvement. SLE has a prevalence of approximately 20–200 per 100 000, occurring most commonly in the Afro-Caribbean population. The American Rheumatism Council criteria for diagnosis are outlined in Box 5.17.

- It is worth being aware of this spectrum of disease and asking about some key areas of symptoms (Table 5.29). Disease damage and activity indices can be assessed by various validated disease activity scores, e.g. the SLE disease activity index.
- Explore her pregnancy expectations.

Feedback to patient

This episode of pericarditis probably supports the possible diagnosis of systemic lupus erythematosus for which you are being investigated. It can cause a range of symptoms including the facial rash and the joint pains, and also pericarditis. Having ensured that the pericarditis symptoms are settling with medication, we should chase the results of all of the tests you have had so far in clinic. I will also let your rheumatologist know that you are here, and if the results do confirm the diagnosis of systemic lupus erythematosus then we should think about treatments to improve things for you. In general, the outlook for pregnancy in systemic lupus erythematosus is good, but the condition should be under good control from the outset of pregnancy, and this is something for the rheumatologist to be aware of and advise on. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Box 5.17 **1997 Revised American Rheumatism Council criteria for diagnosing systemic lupus erythematosus**

1. Malar rash (raised or flat red patches, nasolabial fold sparing)
2. Discoid rash (red papules on head and neck with scaling, follicular keratosis, atrophic scarring and depigmentation)
3. Photosensitivity
4. Oral/nasopharyngeal ulcers (painless)
5. Arthritis (non-erosive, more than two joints)
6. Pleuritis or pericarditis
7. Renal disorder (proteinuria or casts)
8. Neurological disorder (seizures or psychosis)
9. Haematological disorder (haemolytic anaemia, leucopenia, lymphopenia or thrombocytopenia)
10. Immunological serology (anti-double-stranded DNA, anti-Sm antibody, antiphospholipid antibody)
11. Positive antinuclear antibody

Four criteria are required (only one skin manifestation may be used).

Feedback to examiners

Summarise the key history and examination findings

This woman has had a rash and arthropathy symptoms consistent with systemic lupus erythematosus, and now has had an episode of pericarditis.

Provide a diagnosis or differential diagnosis with supporting evidence

She is likely to fulfil the criteria for a diagnosis of systemic lupus erythematosus, especially if autoantibodies for it are positive.

Outline an investigation and management plan

Systemic lupus erythematosus pathogenesis is a complex combination of genetic, hormonal and trigger factors (e.g. infection, ultraviolet radiation, drugs). There is an increased prevalence of human leucocyte antigen A1 B8 DR2 and DR3 in whites with systemic lupus erythematosus. Deficiencies in the classical complement pathway components C1q, C2 and C4 are strongly associated with lupus-like disease. Immunoglobulin G (IgG) receptors on phagocyte cells clear IgG and IgG-containing immune complexes from the circulation, and low-affinity receptors have been found in African American patients. Circulating immune complexes are characteristic in systemic lupus erythematosus

Table 5.29 System review in systemic lupus erythematosus (SLE)

System	Possible features
Non-specific	Fever, fatigue, anorexia, weight loss, lymphadenopathy; CRP usually normal in SLE
Skin (skin involvement affects most patients)	Butterfly rash Alopecia Raynaud's phenomenon Vasculitis Discoid lupus
Musculoskeletal (arthralgia affects most patients)	Symmetrical, flitting and polyarticular arthralgia without synovitis Non-erosive, deforming Jacoud's arthritis more common than erosive arthritis Avascular necrosis of the hip Osteoporosis (vitamin D deficiency, menstrual dysfunction, corticosteroids)
Renal (affect 30%)	Six types of LN: I, minimal mesangial LN; II, mesangial proliferative LN; III, focal LN; IV, diffuse LN; V, membranous LN; VI, advanced sclerosis LN
CNS lupus/neuropsychiatric SLE	Traditionally classified as seizures or psychosis Now the ARC classifies CNS lupus into 19 syndromes, with clear distinction between manifestations of lupus and those due to antiphospholipid syndrome Manifestations include strokes, transient ischaemic attacks, seizures, movement disorders (e.g. chorea), headaches including migraine, cognitive disorders, visual loss, transverse myelopathy and demyelination syndromes (acute demyelinating polyradiculopathy), plexopathy, mononeuropathy, cranial neuropathy Seizures due to lupus cerebral vasculitis rare
Haematological	Around two-thirds have anaemia, usually normochromic normocytic Around one-third have antiphospholipid antibodies Antiphospholipid syndrome
Cardiovascular	Pericarditis commonly subclinical; symptoms in 25% at some stage Myocarditis rare Accelerated atherosclerosis (e.g. coronary, cerebrovascular), independent of traditional CVD risk factors, now recognised as major cause of morbidity and mortality; relative risk increase appears to be around 50
Respiratory	Pleuritic chest pain common, with or without effusions Acute pneumonitis rare but dangerous Chronic pneumonitis common and seldom severe Pulmonary hypertension due to thrombosis or vasculitis 'Shrinking lung syndrome' characterised by dyspnoea and small lungs
Gastrointestinal disease	Oral lesions discoid, erythematous or ulcerative Small-vessel vasculitis can affect gut causing ischaemia, infarction, perforation and peritonitis

ARC, American Rheumatism Council; CNS, central nervous system; CRP, C-reactive protein; CVD, cardiovascular disease; LN, lupus nephritis.

Table 5.30 Treatments in systemic lupus erythematosus (SLE)

Problem	Treatments	Comments
Skin rashes and arthralgia	Sunscreens Topical steroid preparations combined with hydroxychloroquine Topical tacrolimus and pimecrolimus NSAIDs and COX-2 selective agents avoided because of gastrointestinal, renal and cardiovascular risks	Patients with isolated cutaneous, including discoid, lupus are unlikely to progress to systemic disease Hydroxychloroquine is the mainstay for mild SLE with arthralgia, skin rashes, alopecia and oral or genital ulceration; it is well tolerated, disease modifying, has weak antithrombotic action, benefits lipid and glucose profiles and has a low risk of cataracts Oral dapsone is used in resistant skin disease
Lupus nephritis	Long-term high-dose monthly or quarterly intravenous 'pulse' cyclophosphamide traditional Short courses low-dose pulse cyclophosphamide followed by azathioprine similar results with less toxicity Mycophenolate mofetil for induction and maintenance therapy in severe proliferative lupus nephritis promising	Lupus nephritis is a powerful prognostic indicator
CNS lupus/neuropsychiatric SLE	Corticosteroids Immunosuppression (cyclophosphamide, azathioprine) Antipsychotics Anticoagulation for thrombotic manifestations, e.g. stroke, seizures or cognitive dysfunction associated with antiphospholipid antibodies	

CNS, central nervous system; COX-2, cyclo-oxygenase 2; NSAID, non-steroidal anti-inflammatory drug.

and are formed or deposited in the skin, kidney and brain; these activate complement and certain complement fragments (e.g. C3a) and induce release of pro-inflammatory cytokines. Autoantibodies may be present for many years before symptoms but often rise in titre with significant B-cell activation just before symptoms develop. Defective clearance of apoptotic cells may also contribute to the pathogenesis.

An antinuclear antibody titre > 1:80 is present in around 95% of patients. Antibodies to double-stranded DNA are the most common antibodies to an extractable nuclear antigen, positive in most patients. Anti-Sm antibody is highly specific for systemic lupus erythematosus but only positive in around 10% of patients. Antibodies to single-stranded DNA, nucleosomes, C1q, Ro and RNP are also found commonly. Antibodies to double-stranded DNA and nucleosomes probably contribute to the pathogenesis of the disease. Anti-C1q antibodies are important in lupus nephritis and may be useful in detecting flares. Anti-Ro antibodies correlate with photosensitive skin rashes and anti-Ro and La with Sjögren's syndrome. A normal C-reactive protein with a raised erythrocyte sedimentation rate is characteristic in systemic lupus erythematosus.

Mild disease with skin or joint involvement is treated with topical treatments or hydroxychloroquine, moderate disease with non-life-threatening organ involvement (e.g. pericarditis) with corticosteroids and/or steroid-sparing agents and severe disease with life-threatening organ involvement, such as lupus nephritis or central nervous system lupus, with high-dose immunosuppression [Table 5.30]. The prognosis has improved in the past 50 years from 50% 4-year survival to around 85% 10-year survival. This improvement has been brought about in part by optimising the use of hydroxychloroquine, corticosteroids and immunosuppressives (azathioprine, cyclophosphamide and more recently mycophenolate). With an increased knowledge of pathogenesis, biological therapies are emerging (e.g. B-cell depletion, anti-B-cell stimulating factors).

In general, pregnancy outcomes are good if systemic lupus erythematosus is in remission at conception, but there may still be a higher risk of complications. Risk is higher if antiphospholipid antibodies are present. Risk is much higher if active disease, hypertension or lupus nephritis is present at conception, and pregnancy should be deferred until remission. Complications include recurrent early pregnancy loss, fetal death, pre-eclampsia, intrauterine growth restriction and preterm delivery. Maternal thrombosis is increased postpartum, especially in the puerperium.

CASE 5.14 SCLERODERMA

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Karen Longhurst, aged 67 years

This woman is on your ward recovering from pneumonia. She mentions that she has had tightening of her fingers and facial skin for some years.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 67-year-old woman recovering in hospital from pneumonia. You seldom have cause to see a doctor but for some years have noticed that the skin over your hands, face and feet has become more tight and shiny, and you suffer considerably from cold hands and feet. You also felt insidiously more breathless for some months prior to development of the pneumonia. You wonder what might be wrong and what should be done.

Focused history and examination

Initial history

- Ask about symptoms, e.g. pain, tightening skin, shiny skin, Raynaud's phenomenon.
- Ask about the duration of symptoms.

Initial examination

- Examine the face and hands (Box 5.18) for signs of scleroderma.

Box 5.18 **Signs of scleroerma in the face and hands**

Face (Fig. 5.42)

There are *dilated capillaries (telangiectasia)*, and the *skin appears smooth, shiny and tight*. The nose may appear beaked. There may be *perioral skin puckering* with microstomia and restricted mouth opening.

Hands (Fig. 5.43)

The *skin over the fingers is also smooth, shiny and tight (sclerodactyly)*. There may be *dilated nail-fold capillaries (telangiectasia), nail-fold infarcts, ragged cuticles, evidence of digital ischaemia with ulceration, infarcts and pulp atrophy* (+/− amputations), and calcinosis (with subcutaneous calcium deposits in the digits and fingertips).

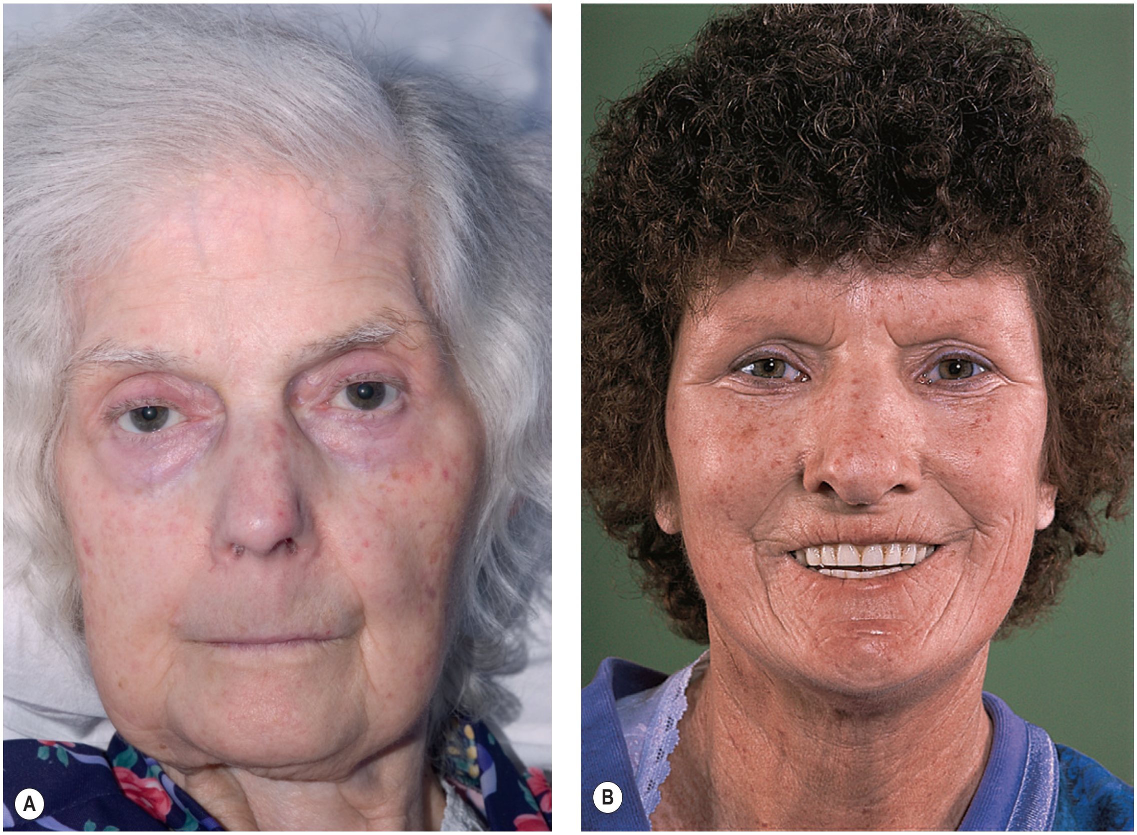


Figure 5.42 (A, B) Scleroderma.

Box 5.19 Important complications of scleroderma

- Interstitial lung disease
- Pulmonary hypertension
- Gastro-oesophageal reflux and Barrett's oesophagus
- Scleroderma renal crisis

Further assessment

- Ask about gastrointestinal symptoms and examine the chest for evidence of interstitial lung disease and signs of pulmonary hypertension. Important complications of scleroderma are listed in Box 5.19.

Although the terms scleroderma and systemic sclerosis (SSc) are often used synonymously, SSc is a heterogeneous disease within the spectrum of scleroderma disorders, SSc being used to describe conditions involving fibrosis of the skin and internal organs with microvasculopathy. SSc is relatively rare with a female–male ratio of 5:1. Scleroderma disorders share several clinical features, notably skin thickening from dermal fibrosis and a high incidence of episodic peripheral vasospasm. The classification of scleroderma is shown in Table 5.31.

- Explore concerns.

Feedback to patient

I think you may have a condition called scleroderma. This is a skin condition that can cause all of the symptoms you have experienced, including a phenomenon called Raynaud's phenomenon in which the hands and feet can go very cold. There is a range of treatments but before starting anything it would be important to do three things. Firstly we should carry out some blood tests to try to establish the diagnosis with certainty. Secondly we should consider running some further tests to examine the possibility of the scleroderma affecting other regions of the body, which it sometimes can, including the lungs and the kidneys. Thirdly we should probably ask a rheumatologist to see you, as scleroderma is an area of their expertise. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman reports typical Raynaud's phenomenon and has telangiectasia, perioral skin puckering with microstomia, sclerodactyly and evidence of digital ischaemia.

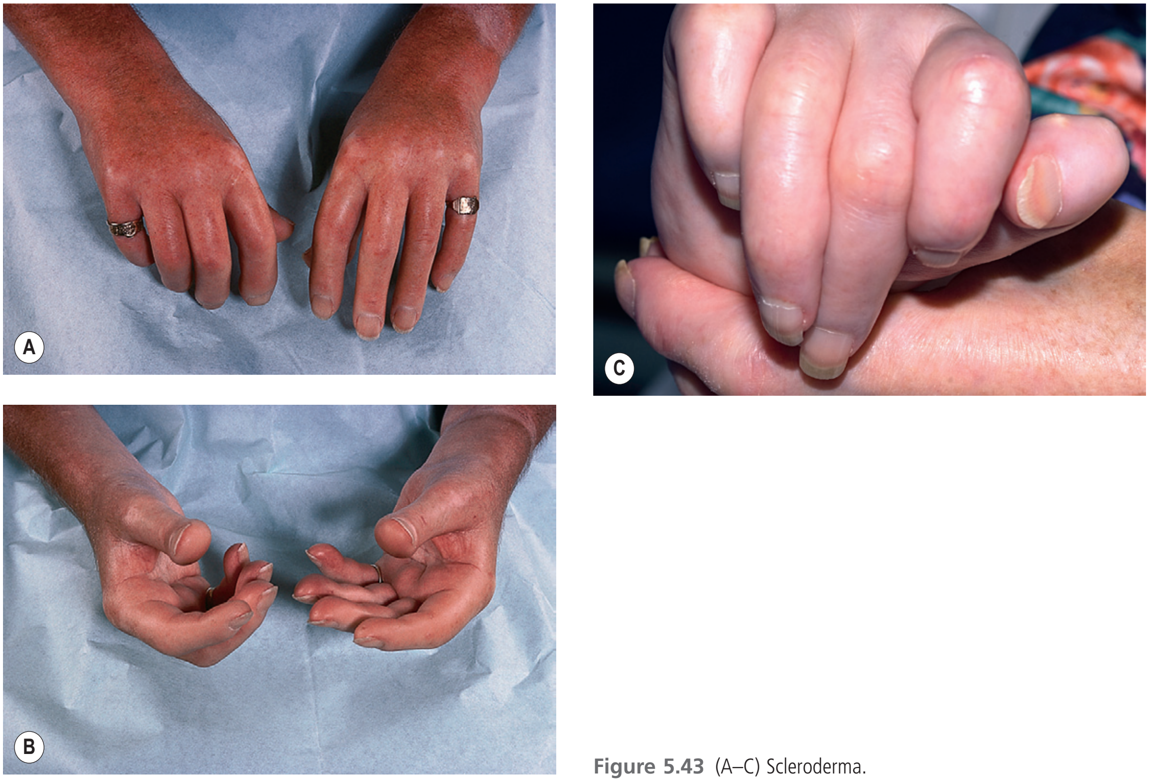


Figure 5.43 (A–C) Scleroderma.

Table 5.31 Scleroderma classification and spectrum of disease

Type	Subtype	Notes
Raynaud's phenomenon	Primary autoimmune	Raynaud's phenomenon in isolation is now thought to sit at one of the spectrum that is scleroderma. In Raynaud's phenomenon there is evidence of microvasculopathy on nail-fold capillaroscopy and / or serum antibodies against nuclear antigens (autoimmune Raynaud's phenomenon), and there is a 10–15% chance of developing a connective tissue disease, including SSc, in the long term. Raynaud's phenomenon affects virtually all patients with SSc, with variable severity. In limited cutaneous (Lc) SSc, it typically precedes other features, but in diffuse cutaneous (Dc) SSc is more likely to be contemporaneous. Raynaud's phenomenon may be secondary to a range of other conditions, including other autoimmune connective tissue disorders, haematological disorders (myeloproliferative, prothrombotic, paraprotein) and occlusive arterial disease.
Systemic scleroderma now more appropriately termed Systemic sclerosis (SSc) Most SSc may be classified as either LcSSc or DcSSc depending upon the extent of skin involvement. Both forms involve other organs.	Limited cutaneous (LcSSc)	This is typically preceded by a long history, often many years, of Raynaud's phenomenon, leading to what used to be referred to as the acronym CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia); the acronym is misleading because it ignores important manifestations of LcSSc such as pulmonary hypertension and gastrointestinal disease.
	Diffuse cutaneous (DcSSc)	This is defined by sclerosis proximal to the elbows or knees or involving the trunk.
	SSc *sine* scleroderma	This refers to a small group of patients with vascular symptoms and SSc-specific antibodies and major organ complications in the absence of significant skin sclerosis
	Scleroderma overlap syndromes	e.g. polymyositis, SLE
Localised scleroderma	Plaque morphea	This refers to plaques of sclerosis, often with purplish edges
	Generalised morphea	This refers to more generalised morphea and is uncommon.
	Linear scleroderma (*en coup de sabre*)	This is uncommon.

Table 5.32 Scleroderma hallmark antibodies

Antigen	Immunofluorescence	Clinical association
Centromere	Centromere	Lc SSc almost exclusively (and occur in 60% of LcSSc) Pulmonary hypertension and gut disease; less likely to have interstitial lung fibrosis
Topoisomerase 1 (Scl-70)	Nucleolar (diffuse fine speckles)	35% of DcSSc, 10–15% of LcSSc Renal disease in DcScc Lung fibrosis in LCSSc or DcSSc
RNA polymerases I and III	Nucleolar (punctuate)	20% of DcSSc Renal disease in LcSSc or DcSSc
Fibrillarin (U3 RNP)	Nucleolar (clumpy)	5% of LcScc or DcSSc Poor outcome in DcScc (cardiac disease, pulmonary hypertension, renal disease)
PM-Scl	Nucleolar (homogenous)	5% of patients – myositis
U1 RNP	Nuclear (speckled)	10% of patients, often black

SSc = systemic sclerosis; LcSSc = limited cutaneous SSc; DcSSc = diffuse cutaneous SSc.
Autoantibody profiles for scleroderma are evolving as the pathogenicity and prognostic implications of some of these are better understood; topoisomerase 1, for example, carries a poorer prognosis.

Table 5.33 Management of scleroderma organ involvement

Organ involved or complication	Clinical manifestations	Investigation	Current treatments
Raynaud's phenomenon (vasospasm + structural changes)	Painful ischaemia Digital ulceration Digital infarction	Capillaroscopy	Vasodilators, e.g. calcium channel blockers Antibiotics Prostacyclin analogues Digital sympathectomy Bosentan Phosphodiesterase inhibitors
Skin	Calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasia	Biopsy seldom needed	Topical emollients Methotrexate for diffuse SSc
			Alternative new strategies may include anti-thymocyte globulin followed by mycophenolate mofetil and high-dose cyclophosphamide and then autologous peripheral stem cell transplantation. However, diffuse SSc can sometimes strikingly improve by 3 years without treatment
Lung	Interstitial lung disease (SSc-ILD) Pulmonary hypertension	Pulmonary function tests (DLCO the best predictor of survival) High-resolution CT scan (correlates well with DCLO) Bronchoalveolar lavage (heavy neutrophil counts associated with severe disease) Echocardiography Cardiac angiography (mean PAP > 25 mmHg at rest and > 30 mmHg on exercise)	Cyclophosphamide Long-term oxygen therapy Diuretics Anticoagulation Epoprostenol Bosentan Atrial septostomy Lung transplantation (late stage)

Table 5.33 Management of scleroderma organ involvement—cont'd

Organ involved or complication	Clinical manifestations	Investigation	Current treatments
Gastrointestinal tract	Gastro-oesophageal reflux Oesophageal dysmotility Bacterial overgrowth Vascular mucosal lesions Constipation / diarrhoea	Endoscopy	Proton pump inhibitors Prokinetic agents Antibiotics
Kidney	Scleroderma renal crisis This is most common in early diffuse SSc with rapid skin progression, often associated with anaemia, anti-RNA polymerase I and III antibody positivity and antecedent use of high-dose steroids, NSAIDs and ciclosporin. It presents with abrupt severe hypertension with headache and visual disturbance and accelerated oliguric renal failure with a nephritic picture. Flash pulmonary oedema, heart failure and pericardial effusions may occur. Microangiopathic haemolytic anaemia or thrombocytopenia is possible	Urinalysis Renal biopsy (fibrinoid necrosis; true vasculitis rare)	This is the most important renal complication, and was the major cause of mortality before angiotensin-converting enzyme inhibitors (survival 10% at 1 year without treatment to 65% at 5 years with treatment)
Cardiac	Conduction disturbance		Permanent pacemaker

Genetic abnormalities in anti-fibrillin-1 are implicated in scleroderma. The pathogenesis is incompletely understood, but three mechanisms are involved: vascular, with endothelial cell activation; immunological, with perivascular inflammation with monocyte and subsequent lymphocyte infiltration; fibrosis, with fibroblast activation and deposition in affected tissues and organs. These mechanisms explain the vascular and immune therapies in scleroderma, and anti-transforming growth factor antibody and endothelin receptor antagonists are emerging anti-fibrotic treatments. CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; NSAID, non-steroidal anti-inflammatory drug; PAP, pulmonary artery pressure; SSc, systemic sclerosis.

Provide a diagnosis or differential diagnosis with supporting evidence

She has features of scleroderma, and the breathlessness over the past few months raises concern about systemic sclerosis with either pulmonary fibrosis or pulmonary hypertension.

Outline an investigation and management plan

I would arrange for her to have a range of blood tests including scleroderma hallmark antibodies [Table 5.32], pulmonary function tests and echocardiography and possibly consider chest imaging.

Interstitial lung disease and pulmonary hypertension are major causes of mortality and morbidity in systemic sclerosis.

The prevalence of pulmonary hypertension in systemic sclerosis is probably 7–15% with a 5-year survival of 10% compared with 80% in those without pulmonary hypertension. It may occur with both limited systemic sclerosis with anti-centromere antibody positivity and diffuse systemic sclerosis with antifibrillarin antibodies (U3RNP). Exertional dyspnoea is the major symptom, but diagnosis is often delayed, with subsequent right heart failure. General measures include oral anticoagulation, diuretics and oxygen. Intravenous prostacyclin (epoprostenol) improves exercise capacity, cardiac output and survival but has practical limitations and other prostacyclin modes of administration appear less effective. PDE5 inhibitors (e.g. sildenafil) may be used. The oral endothelin receptor antagonist bosentan may be used, sometimes combined with intravenous prostacyclin and sildenafil in severe disease. Patients with systemic sclerosis should have annual echocardiography and pulmonary function tests, because a reduced transfer factor of the lung for carbon monoxide (< 60% predicted) with a normal forced vital capacity may indicate subsequent development of pulmonary hypertension.

Symptoms of lung fibrosis are usually late. Cyclophosphamide is the current drug of choice.

Other important complications of scleroderma include gastro-oesophageal reflux and kidney disease [Table 5.33].

CASE 5.15 CRYSTAL ARTHROPATHY

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Mr Robert Warrell, age 64 years
>
> This man has presented to the acute medical unit with a painful, swollen foot.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 64-year-old man who has been referred to the hospital with an exquisitely painful, swollen foot, especially around the first metatarsal joint. You have had this once in the past, though not as severe, and it responded to anti-inflammatory drugs. You are known to have tophaceous gout. You have taken allopurinol for tophaceous gout in the past and decided to restart this when the foot became painful, but it seemed to make the foot worse.

Focused history and examination

Initial history

- Ask about previous symptoms or any history of confirmed gout.
- Ask about any injury to the foot, historic or recent, and in particular any breach of skin (septic arthritis).
- Ask about any treatment received.

Initial examination

- In acute gout there is *swelling of the first metatarsophalangeal (MTP) joint* (or knee, ankle or other joints). The patient reports that the joint has been *exquisitely painful and tender* (ask before examining!). Weight bearing is very painful.
- In chronic tophaceous gout (Fig. 5.44) there are *painless tophi* – cheesy, chalky lesions that may ulcerate – at extra-articular sites (helix, olecranon/patellar bursa, ulnar surface of forearm, Achilles tendon, etc.). Polyarticular involvement is also common, e.g. knees, first MTP joint, ankles, hands.

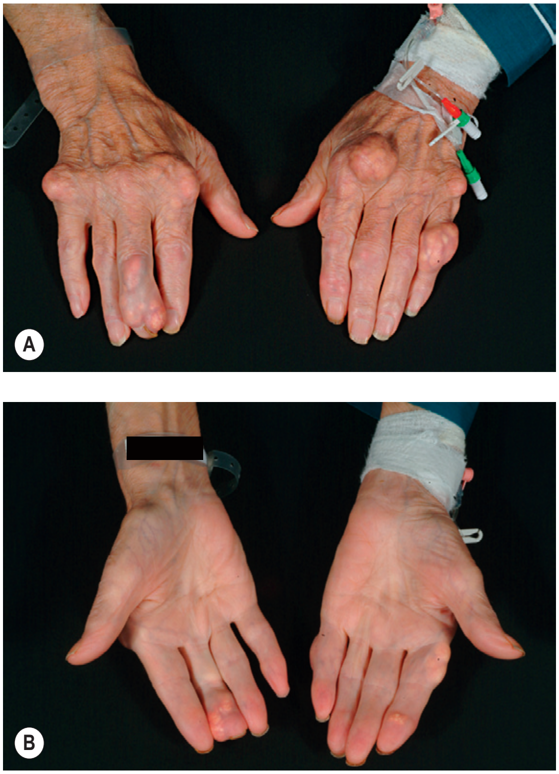


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Figure 5.44 (A, B) Tophaceous gout.

An acute monoarthritis that is exquisitely tender and with associated erythema is invariably the result of gout or septic arthritis. Acute gout is the result of an intense inflammatory response in joints (tophaceous gout is non-inflammatory) and there may be fever and systemic upset. The crystal arthropathies include gout, pseudogout and, rarely, calcium phosphate arthropathies (Table 5.34).

Further assessment

- Enquire about causes and risk factors for gout (Table 5.35), although many cases are idiopathic.
- Explore his understanding of allopurinol.

Feedback to patient

> I think this is almost certainly acute gout, which is due to uric acid crystals in one or some of the joints. There is a small possibility of an infected joint. We should arrange some bloods and an X-ray of the foot, and monitor for signs of fever. If symptoms are settling with treatment (anti-inflammatories) then we can be reassured but if things are getting worse then I would ask one the orthopaedic specialists to have a look at the joint and possibly take a sample of fluid from it to exclude infection. The tophaceous gout that you have had is not necessarily associated with acute gout (many people with tophaceous gout will never get acute gout) but is worth taking

Table 5.34 The crystal arthropathies

Arthropathy	Crystal	Notes
Gout	Urate in joint or soft tissues	Described in text.
Pseudogout	Calcium pyrophosphate (shed from joints)	This can mimic gout. It often affects the wrist, knee or shoulder but may be polyarticular. Chondrocalcinosis (calcium deposition in cartilage) is an essential precursor, but also occurs in gout, primary hyperparathyroidism, hypothyroidism and haemochromatosis – states promoting cartilage calcification. Synovial fluid is similar to that of gout but crystals are polymorphic, often rhomboid or rectangular, sometimes needle shaped, and positively birefringent. It is very rare under the age of 50 years. Treatment is as for acute gout, but prophylaxis is unavailable.
Basic calcium phosphate arthopathies – calcific periarthritis, Milwaukee shoulder	Calcium hydroxyapatite	Calcific periarthritis is a rotator cuff problem that tends to occur in midlife. Milwaukee shoulder is a very severe, rapidly destructive calcium hydroxapatite shoulder arthritis in older people.

Table 5.35 Gout – causes and risk factors

Cause or risk factor	Examples
Sex	Male > female
Family history	Genetics and ethnicity, e.g. more common in Maori population (gout was also common in *Tyrannosaurus rex*!)
Metabolic syndrome	Obesity, increased cholesterol and hypertension within metabolic syndrome
Drugs	Alcohol Diuretics Allopurinol Low-dose aspirin / salicylates Ciclosporin / cytotoxics Levodopa Ethambutol, pyrazinamide
Diet (usually in setting of underexcretion)	Excess purines, e.g. beer, shellfish, liver
Dehydration	
Underexcretion (the major group of causes) of urate	Sepsis (lactic acid competes with urate excretion) Chronic kidney disease (creatinine clearance < 30% of normal) Hypothyroidism Drugs Lead
Overproduction of urate	Myeloproliferative or lymphoproliferative disease Tumour lysis / chemotherapy Chronic haemolysis Inborn errors increasing purine levels

Acute gout is most readily induced when serum urate levels are in a state of rapid flux, rather than by absolute levels, and can occur when the level is falling. Chronic tophaceous gout tends to affect an older age group and is more readily associated with longstanding high serum urate levels. There tend to be exacerbations and remissions. Uric acid is less soluble at lower temperatures, which may explain the tendency for tophi to occur at sites exposed to cold.

preventive medication for, although we should not start any preventive medicine until the acute gout is cleared up. Indeed allopurinol, whilst good at preventing gout and preventing progressing of chronic tophaceous gout, can make acute gout worse. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has evidence of tophaceous gout and has probably had an episode of acute gout, possibly worsened acutely by allopurinol.

Provide a diagnosis or differential diagnosis with supporting evidence

Sepsis is important to exclude, and pseudogout can often mimic gout clinically although the knee and ankle are more commonly affected in pseudogout than the toes.

Outline an investigation and management plan

Synovial fluid should be aspirated whenever possible (large joint) and demonstrates inflammation (often with a very high white cell count); polarised microscopy reveals needle-shaped, negatively birefringent intracellular (especially acute) and extracellular (especially ulcerated tophi) crystals. Serum urate levels can be misleading. Inflammatory markers are raised; a C-reactive protein in the range 50–150 is typical; higher levels suggest sepsis. X-rays may show periarticular punched-out erosions and eventually joint destruction. Tophi are usually radiolucent but sometimes calcified.

Rehydration is important. Any implicated drug should be stopped. Non-steroidal anti-inflammatory drugs alleviate symptoms; indometacin 50 mg four times daily for 3 days, decreasing by 50 mg every 2 days thereafter, is very effective. Cyclo-oxygenase 2 agents (etoricoxib) are of proven efficacy but contentious. Colchicine is useful if non-steroidal anti-inflammatory drugs are contraindicated, e.g. 0.5 mg twice or thrice daily (not more frequently as was once recommended). Prednisolone 15 mg, reducing over 10 days, is also effective, and corticosteroid joint injections can be used. Biological treatments offer novel possibilities as the pathophysiology becomes better understood. Painful acute attacks would last several weeks without treatment.

As well as tackling reversible causes or risk factors, allopurinol is effective for recurrent gout. Treatment should be covered for 6 weeks or so with colchicine or non-steroidal anti-inflammatory drugs because allopurinol can precipitate acute gout. Allopurinol titration to serum urate levels is currently favoured, a typical dose 300 mg but up to 600 or 900 mg may be needed and a reduction to 100 mg in patients with chronic kidney disease. Allopurinol use should be decided with the patient, but two to three attacks is generally a convincing reason as joints become irreversibly damaged by repeated attacks of inflammation. Other indications include a single polyarticular attack, tophaceous gout, urate calculi and renal disease. Nephrolithiasis and renal failure are caused by urate crystals formed by prolonged hyperuricaemia and hyperuricuria. New drugs such as febuxostat may prove useful for those who cannot tolerate allopurinol.

CASE 5.16 OSTEOARTHRITIS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Katherine Grimshaw, aged 76 years

This woman is on your ward recovering from a myocardial infarction. She asks if she can have some treatment for her painful hands.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 76-year-old woman in hospital following a heart attack. You suffer from chronic pain in your hands and knees that you have always attributed to arthritis and want to know if some painkillers can be prescribed. You are also concerned because you have had considerable knee pain in the past and seen an orthopaedic surgeon who said you had some arthritis of the knee but that it did not warrant surgery and that your X-rays were really not that bad.

Focused history and examination

Initial history

- Ask about symptoms, e.g. pain, swelling, distribution, duration.
- Ask about any provoking and relieving factors.
- Ask about any treatment.

Initial examination

- There is *bony swelling* of the *distal interphalangeal joints (Heberden's nodes)* (Fig. 5.45) and *proximal interphalangeal joints (Bouchard's nodes)*. There is not usually evidence of synovitis. There may be crepitus and restricted range of movement. There is no apparent systemic upset.

Further assessment

- Consider the features in Table 5.36 to confirm the likelihood of osteoarthritis. Osteoarthritis pain is worse with activity. Any morning stiffness is usually brief, unlike inflammatory arthritis.

Osteoarthritis is restricted to synovial joints, typically in the hands and spine (especially C5, L3, L4), and the hips

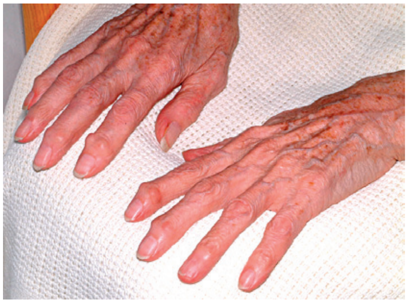


Figure 5.45 Heberden's nodes.

Table 5.36 Pointers to other diagnoses

Clinical features	Associations
Age < 45 years	Inflammatory arthritis
Marked early morning stiffness	Inflammatory arthritis
Joint locking/giving	Meniscal tear
Regional pain	Fibromyalgia
Swelling adjacent to joint	Bursitis

Box 5.20 **Risk factors for and causes of osteoarthritis (OA)**

Generalised predisposition

- Age
- Gender (females > males for hand and knee, females < males for hip)
- Hereditary (genes not yet identified)
- Obesity

Localised / biomechanical predisposition

- Joint injury / 'wear and tear'
- Surgery
- Muscle weakness

OA is the most common joint disease, its impact set to grow as the prevalence of obesity and the elderly population rises. Many clinicians regard it as simply a disease of 'wear and tear', by implication not modifiable. Such prejudices have led to significant academic apathy in it, impeding understanding of its pathogenesis, adequate classification and the development of sensitive tools for diagnosis and prognostic assessment. The recent identification of key degradative enzymes in cartilage and the use of mouse models to study its pathogenesis are changing things, and will hopefully advance understanding and treatment of OA.

OA is a disease of joint damage and repair via osteophyte formation, bone remodelling, synovial responses and capsular change – only synovial joints are affected, with loss of cartilage and damage beneath. What provokes the process is unclear. OA may be dynamic, equivalent to diverticulitis, with flares and remissions. We may also be looking at the wrong pathology radiologically – appearances of which do not correlate with symptoms. OA is now viewed as a disease where risk factors induce subtle changes in joint shape and stability leading to attempted repair. This may have one of two outcomes – a successful, compensated joint without pain or disability, or a failed, decompensated joint with symptoms and disability. There seem to be three categories of patient – those with developing disease (painful), those with stable disease (painless) and those with progressive disease (painful) – all of which have the same radiological appearances. The cause of pain is less certain, e.g. the ankle is never really affected but often painful; the elbow is often affected but seldom painful; the knee can be highly symptomatic with minimal damage. Pain tends to occur only when joint anatomy is changing. The natural history varies between individuals and joint sites.

OA may be a disorder of accelerated evolution – affected joints tend to be those that have changed as we have evolved from tree-dwelling monkeys and apes to upright humans, and there is no evolutionary pressure to protect joints after reproductive age. Animals tend not to develop osteoarthritis, or if they do it involves specific types, e.g. hip dysplasia in dogs and horses of certain breeds.

and the knees. Risk factors for and causes of are listed in Box 5.20.

- Consider other complications of osteoarthritis, including ankylosis, peripheral nerve entrapment (e.g. carpal tunnel syndrome) and cervical spondylosis with cervical myeloradiculopathy.
- Explore her concerns about her knee pain.

Box 5.21 **Treatments for osteoarthritis**

Non-pharmacological

- Education
- Weight reduction
- Physiotherapy (exercise is probably more beneficial than anything, with emerging evidence of joint improvement)

Oral, topical and intra-articular drugs

- Paracetamol
- Non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 inhibitors, co-prescribed with a proton pump inhibitor
- Topical NSAIDs for hand or knee arthritis
- Intra-articular steroids
- Intra-articular viscosupplemtenation not deemed beneficial

Dietary

- Glucosamine sulphate (synthetic cartilage matrix molecule) and chondroitin – modest questionable benefit, to be discontinued if no improvement

Surgery

- Total joint replacement
- Arthroscopic lavage and debridement not deemed useful unless mechanical locking

Disease modification

- So far elusive, but some evidence for strontium ranelate

Feedback to patient

This is absolutely osteoarthritis in the hands, due partly to 'wear and tear' of the joints, although we don't yet understand the exact cause of the condition. As you say painkillers can help, in the first instance, relatively simple ones often all that is necessary. The knee pain may well be due to osteoarthritis, and it would be sensible for me to review the summary from the orthopaedic surgeon. The peculiar thing about osteoarthritis is that the degree of symptoms does not relate to the degree of damage seen on X-ray and some people can have very minor structural changes in the knee and yet an awful lot of pain. In these circumstances it is always worth considering the possibility of other diagnoses although I am reasonably confident that there is nothing more sinister going on. However you and your general practitioner may need to think about the range of treatments now available for osteoarthritis pain should the knee become more troublesome again in future. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has Heberden's and Bouchard's nodes.

Provide a diagnosis or differential diagnosis with supporting evidence

She has osteoarthritis.

Outline an investigation and management plan

Structural abnormalities are exceedingly common radiologically. Almost all people over 50 years of age will have some osteophytes; progression to loss of joint space and subchondral bone sclerosis and ultimately a damaged looking joint are characteristic of osteoarthritis. Prevention is important. Some types of physical activity are associated with an increased risk of arthritis in certain joints. Previous knee injury, surgery and even occupational or habitual kneeling and squatting can, for example, predispose to osteoarthritis. Treatments include physiotherapy and drug therapies [Box 5.21].

CASE 5.17 PAGET'S DISEASE

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Peter Hancock, aged 65 years

This man is in hospital receiving treatment for a soft-tissue infection but mentions that his hearing has not been as good in the past few months.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 65-year-old man in hospital with a deep skin infection, but recovering well. You have Paget's disease although have not been on any treatment. You feel that in the past few months your hearing has been less good in both ears and mention this to the doctor.

Focused history and examination

Initial history

- Ask whether the hearing loss occurred suddenly or slowly, and if it seems to be unilateral or bilateral.
- Ask about associated symptoms such as vertigo, facial sensory loss or facial weakness or headaches.
- Ask about a previous diagnosis of Paget's disease and ask about bone pain.

Initial examination

- Look for *enlargement of the skull* (Fig. 5.46) or if there is *bowing of the tibia* (Fig. 5.47), and feel if the skin over the leg is warm. There may be kyphosis.

Further assessment

- Consider other features and complications of Paget's disease (Box 5.22). Check for the bounding pulse of hyperdynamic circulation.
- Explore the functional consequences of his deafness.

Feedback to patient

There is a possibility that the change in hearing is due to Paget's disease. This can occur if enlarged bone is pressing on nerves controlling hearing. There are many other possibilities but if due to Paget's then this needs to be identified as soon as possible and treatment for the Paget's considered. In the first instance we should examine the ears with an otoscope (torch) and arrange an audiogram or special hearing test. If these confirm that the problem is likely to be due to compression of the nerves and not something else such as a build-up of wax or fluid, then we should arrange a scan of the auditory apparatus and seek specialist opinions from ear, nose and throat and rheumatology experts. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has bony skull enlargement together with bilateral hearing loss that is probably sensorineural.

Provide a diagnosis or differential diagnosis with supporting evidence

He has Paget's disease.

Outline an investigation and management plan

Serum and urine biochemical changes in Paget's disease include raised alkaline phosphatase, raised serum osteocalcin (but often normal, and not used in practice) and raised urinary hydroxyproline and pyridinolone (markers of bone resorption, and not used in practice). Other causes of raised alkaline phosphatase include hyperparathyroidism, bone metastases, growth, osteomalacia and liver disease.

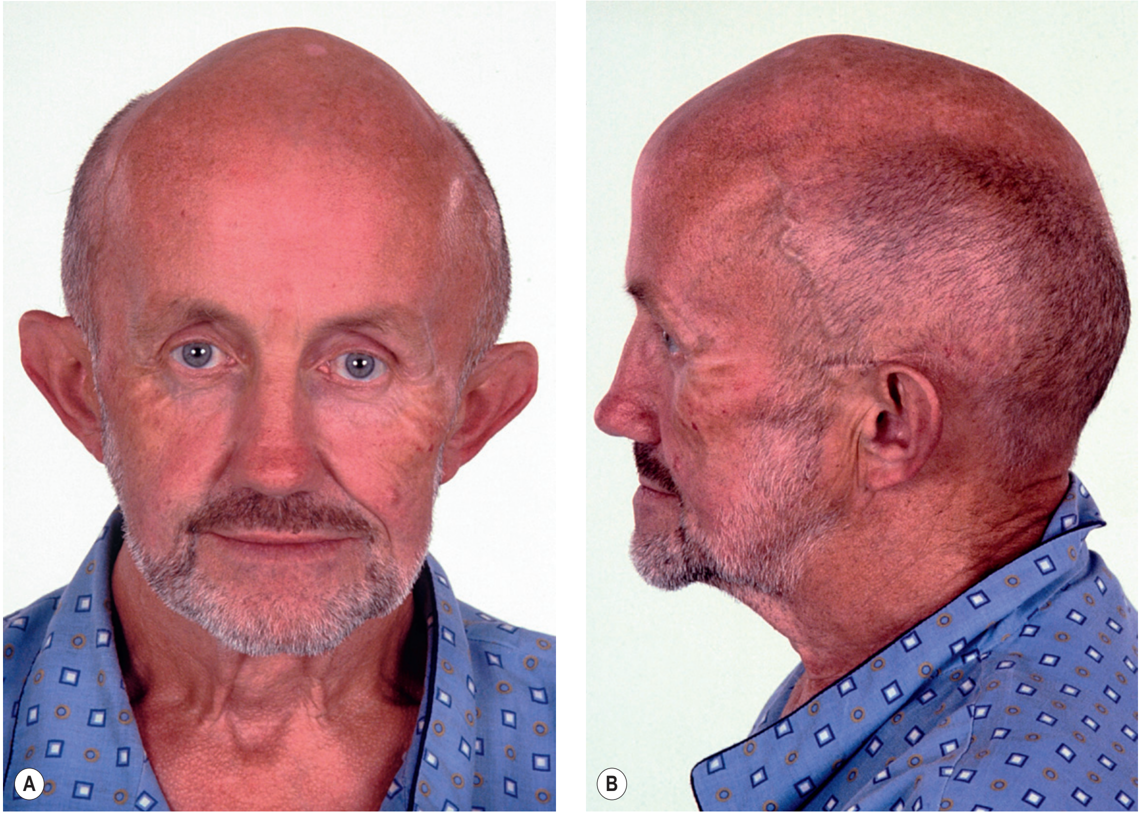


Figure 5.46 (A, B) Paget's disease of the skull.

Box 5.22 **Features and complications of Paget's disease**

- Skeletal deformity and increased fracture risk
- Neurological compression syndromes caused by bone enlargement, e.g. closure of skull foramina causing deafness
- High-output cardiac failure
- Osteosarcoma (rare)

Paget's disease is caused by focal or multifocal areas of bone resorption by large osteoclasts, followed by increased bone formation, but the new bone is abnormal, with a mosaic appearance on microscopy. It is expanded in size, deforms and fractures more easily and is highly vascularised. Pathological changes tend to progress through bone at a rate of around 1 cm per year, but do not advance from bone to bone. Radiographic evidence of Paget's disease is seen in around 2.5% of men over 55 years of age, and a little less in women. Less than 10% of those have symptoms. It occurs predominantly in people of white British origin.

Radiology confirms Paget's disease bone expansion. This is rare in metastases, which tend to be sclerotic but not expanded. Uncertainty is occasionally resolved by bone biopsy, for example in a case of isolated rib expansion.

Common indications for treatment of Paget's disease are bone pain or hypercalcaemia, although the latter tends to occur only in immobilised patients.

There is no absolute consensus about treatment of asymptomatic Paget's disease, but indications to treat include skull disease (risk of deafness or progression of), long-bone disease (risk of deformity, fracture and arthritis) or spinal disease (risk of cord compression or vascular steal syndrome).

Bisphosphonate therapy (intravenous pamidronate, oral risedronate or intravenous zoledronic acid) is the treatment of choice, with a view to normalisation of alkaline phosphatase levels (achieved in around 75% of patients); this is associated with marked pain reduction.

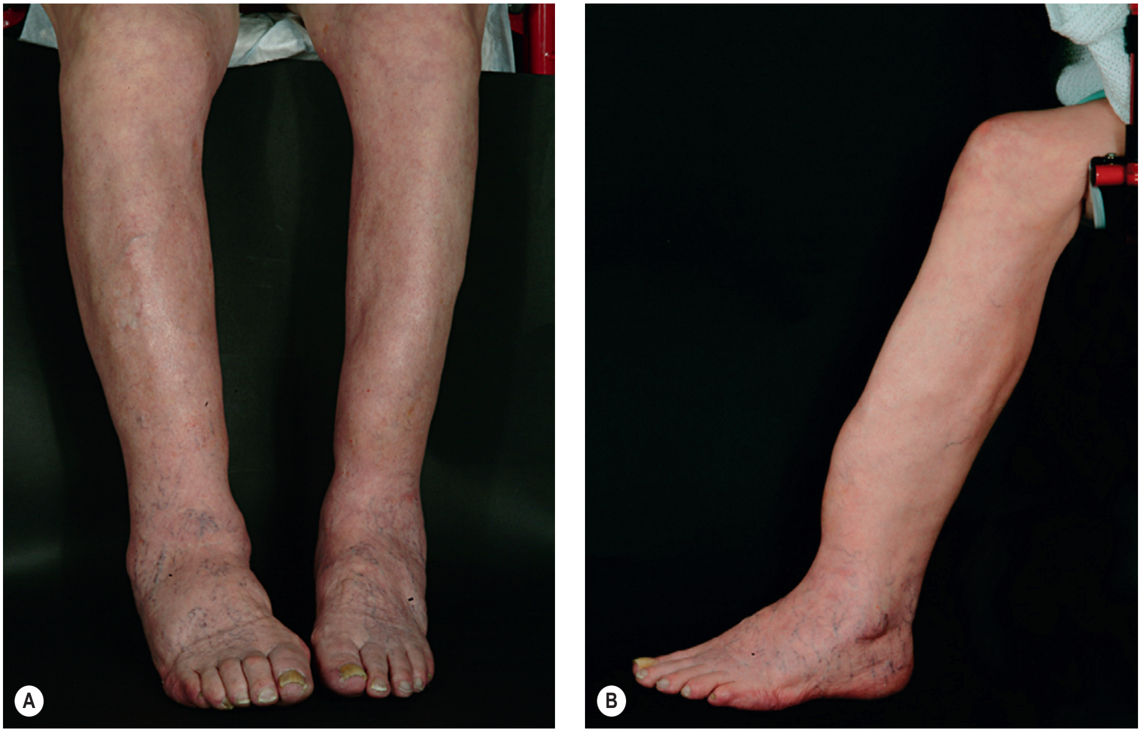


Figure 5.47 (A, B) Paget's disease of the tibia.

CASE 5.18 MARFAN'S SYNDROME

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

> Re: Mr David White, aged 29 years
>
> This man is in your clinic because his general practitioner is concerned about the possibility of Marfan's syndrome. He has recently seen a cardiologist because of a murmur.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 29-year-old man in clinic because your general practitioner (GP) is concerned about the possibility of Marfan's syndrome. You have seen a cardiologist who mentioned the possibility of mitral valve prolapse, and an echocardiogram has been arranged. You are previously very healthy and went to see your GP originally because of ankle pain. You are now very worried.

Focused history and examination

Initial history

- Explore what he has been told so far by the cardiologist.
- Ask about the ankle pain, and a history of musculoskeletal problems including joint laxity.
- Ask about a family history of tall stature and long arms and fingers.

Initial examination

- He is *tall*, with a *thin body habitus*, *long limbs*, *arachnodactyly* and a *pectus deformity*. There is a *high-arched palate* with dental crowding (Fig. 5.48).

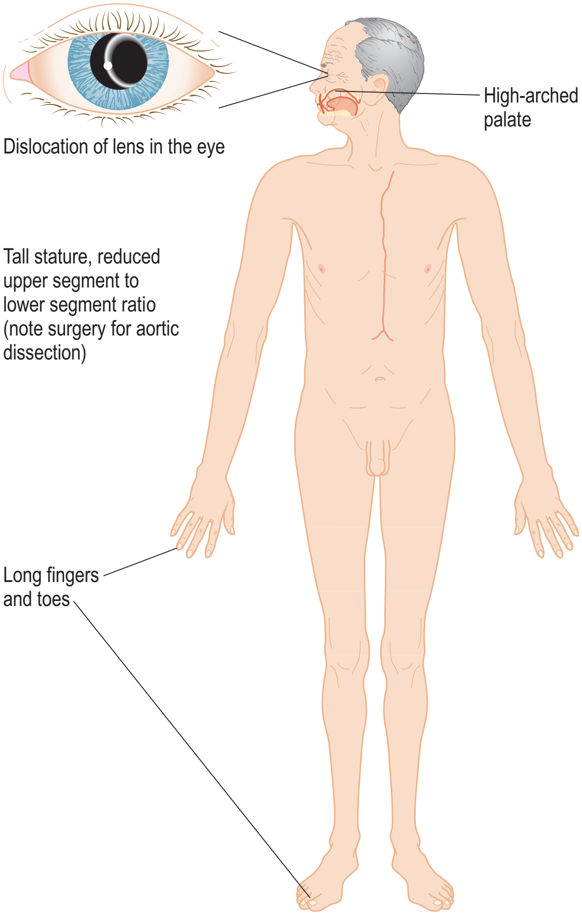

Dislocation of lens in the eye
High-arched palate
Tall stature, reduced upper segment to lower segment ratio (note surgery for aortic dissection)
Long fingers and toes

Figure 5.48 Marfan's syndrome.

Further assessment

- Ask about eye problems.
- Examine briefly for a high-arched palate.
- Auscultate the precordium for evidence of aortic regurgitation or mitral valve prolapse (very common, often with regurgitation).

To formally confirm a diagnosis of Marfan's syndrome, reference is made to the Ghent diagnostic nosology devised in 1996 in which clinical features are assessed as part of seven body 'systems' (Table 5.37) to determine whether that system provides a major criterion or simply system involvement. Plainly this is not to be memorised, unless you are exceptionally unimaginative with little better to do, have a peculiarly agile memory, or are odd in other ways.

Differential diagnoses of Marfan's syndrome on the basis of skeletal, cardiac and ocular manifestations include a range of genetic disorders such as homocystinuria, Ehlers–Danlos syndrome, ectopia lentis, Beal's syndrome, Marshall–Stickler syndrome and the MASS phenotype. There is a range of Marfan-like disorders with the presence of fibrillin mutations without Marfan's syndrome. These have a good prognosis, and include MASS (mitral valve prolapse, mild non-progressive aortic dilatation, skin and skeletal features).

- Explore his concerns.

Feedback to patient

There is a possibility that you have a condition called Marfan's syndrome as your general practitioner suggested to you. This is a genetic disorder of elastic fibres that occur in various tissues of the body, including the skin, and sometimes the heart and eye. The most common heart problem is mitral valve prolapse, which I suspect you have, but mitral valve prolapse, in which part of one of the heart valves is a little floppy, is a very common finding in the general population and often of no significance. The other thing to mention is that Marfan's syndrome has a wide spectrum from being very mild to being much more severe, and the fact that you have reached 29 years of age without it being diagnosed is noteworthy; some people only ever have very limited manifestations. The first things to do, I feel, are to confirm whether or not there is any trouble with one of the heart valves by way of the heart scan, and to try to determine if the possibility of Marfan's syndrome is confirmed with further tests. It is very much a specialist condition and we would arrange for an expert in it to see you and talk it through with you in some detail. I'd be happy to talk about any of this in more detail as best I can or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has some evidence of joint laxity, and is tall with long arms and fingers. He has evidence of mitral valve prolapse.

Provide a diagnosis or differential diagnosis with supporting evidence

These features would suggest a need to investigate further for a diagnosis of Marfan's syndrome, and there are detailed criteria embracing skeletal, eye, heart, lung and skin manifestations together with genetics. Some people have a limited condition called the MASS phenotype with mitral valve prolapse, mild non-progressive aortic dilatation, skin and skeletal features. However there are more serious manifestations of Marfan's syndrome such as valve regurgitation and aortic dilatation.

Outline an investigation and management plan

Referral to a clinical geneticist is important, as is liaison with the cardiologist about his valvular condition. He needs expert guidance about diagnosis

Table 5.37 Diagnostic criteria for Marfan's syndrome

	Major criteria	Minor criteria	For involvement	Diagnosis
Skeletal system	≥ 4 of: Pectus carinatum Pectus excavatum needing surgery Reduced upper-segment to lower-segment ratio or arm span to height ratio Wrist and thumb signs Scoliosis > 20° or spondylolisthesis Reduced extension of elbows (< 170°) Medial displacement of medial malleolus causing pes planus Protrusio acetabulae of any degree on X-ray	Pectus excavatum Joint hypermobility High arched palate with crowded teeth Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)	≥ 2 features contributing to major criteria or 1 feature contributing to major criteria and 2 minor criteria	
Ocular system	Ectopia lentis	Flat cornea Increased axial length of globe Hypoplastic iris or ciliary muscle causing decreased miosis	≥ 2 minor criteria	**Index case** If family/genetic history not contributory, major criteria in two or more different organ systems and involvement of a third are needed; if a mutation is identified, one major criterion in a organ system and involvement of a second are needed for diagnosis.
Cardiovascular system	*Either* dilatation of ascending aorta with or without regurgitation, and involving at least sinuses of Valsalva (echocardiography) *or* dissection of ascending aorta	Mitral valve prolapse with or without regurgitation Dilatation of main pulmonary artery without alternative cause if younger than 40 years Calcified mitral annulus if younger than 40 years Dilatation or dissection of descending thoracic or abdominal aorta if younger than 50 years	1 minor criterion	**Relative of an index case meeting diagnostic criteria** The presence of a major criterion in the family history, one major criterion in an organ system and involvement of a third are needed for diagnosis.
Pulmonary system	None	Spontaneous pneumothorax Apical blebs	1 minor criterion	
Skin and integument	None	Striae atrophica (stretch marks) without marked weight gain, pregnancy or repetitive stress Recurrent or incisional herniae	1 minor criterion	
Dura	Lumbosacral dural ectasia (very common and identified by MR imaging if presence would make diagnosis)	None		
Family/genetic history	Parent, child or sibling meeting criteria independently Mutation in FBN1 Haplotype around FBN1 associated with Marfan's in family	None		

Marfan's syndrome is a variable, autosomal dominant connective tissue disorder with an incidence of around 1–2 in 10 000. It affects both sexes equally. A fundamental problem is a decreased elastin content in tissues, and fragmentation of elastic fibres, due to mutations in the extracellular matrix protein fibrillin-1 (FBM1) located on chromosome 15. Mutations are not always detectable in people with Marfan's syndrome and furthermore may be found in people without Marfan's syndrome. Family history is negative in around 25% of cases, probably explained by sporadic mutations. Modern understanding is that many aspects of the disorder are caused by altered regulation of transforming growth factor-β, highlighting a therapeutic potential for transforming growth factor-β antagonists.

Table 5.38 Management of complications in Marfan's syndrome

Aortic root dilatation	Beta blockers reduce the elastic fibre degeneration in the aorta that causes progressive dilatation, aortic valve incompetence, aneurysms and aortic dissection. The type of fibrillin mutation determines the severity and rate of progression and, if medical treatment fails and the aortic root dilates to 5.5 cm or more, prophylactic surgery is considered. As patients are surviving longer, second aneurysms and second operations are not uncommon. Life expectancy remains 45 +/− 17 years, with scope for improvement. Aortic dissection is associated with an aortic diameter exceeding 5.5 cm, a rate of dilatation exceeding 5% or 2 mm per year or a history of aortic dissection. The major risk in pregnancy is aortic dissection, greatly increased, especially if the aortic root diameter exceeds 4 cm, probably because of collagen and elastin deposition inhibition by oestrogens and hyperdynamic circulation.
Ocular manifestations	Bilateral ectopia lentis occurs in around 25% of patients. Lens dislocation may occur. Myopia is associated with an increased risk of retinal detachment. Regular ophthalmic assessment is needed.
Skeletal manifestations	Common problems are joint laxity with arthralgia and myalgia (> 50% of cases), scoliosis and reduced bone mineral density. Avoidance of contact sports protects joints and the lens of the eye from dislocation.
Respiratory manifestations	Pectus excavatum occurs in two-thirds of patients, and can sometimes cause restrictive ventilation requiring surgery. Spontaneous pneumothorax occurs in up to 10% of patients, and patient awareness is essential. Scuba diving should be avoided because of the risk of pneumothorax.

and assessment for and management of any complications [Table 5.38], and counselling about the genetic basis of the condition.

CASE 5.19 EHLERS–DANLOS SYNDROME

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Mr Donald Brown, aged 35 years
>
> This man has been admitted to the acute medical unit with acute chest and back pain. His symptoms have settled somewhat, he is cardiovascularly stable and his electrocardiogram is normal.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old man with known Ehlers–Danlos syndrome. You developed severe chest and back pain this morning and have been admitted to the hospital. You are feeling better after analgesia and the pain is now localised to the mid-thoracic spine. You will also mention to the doctor concerns about increasing falls as a result of the ligament laxity in your feet.

Focused history and examination

Initial history

- Ask about past medical history and confirm Ehlers–Danlos syndrome.

Initial examination

There may be a combination of three broad clinical features:

- *Purpura* and skin fragility with poor 'tissue-papery' wound healing (Fig. 5.49)
- *Skin 'stretchiness'* which later becomes lax with extensive folds and wrinkles
- *Joint hypermobility*, and kyphoscoliosis.

Ehlers–Danlos syndrome refers to a heterogeneous range of disorders with autosomal dominant, autosomal recessive or X-linked inheritance. In classic Ehlers–Danlos syndrome with gross joint laxity and skin hyperextensibility, disease is principally the result of mutations in genes encoding collagen type V (*COL5A1* and *COL5A2*). In a vascular type of Ehlers–Danlos syndrome, collagen type III (*COL3A1*) results in arterial rupture, e.g. gastrointestinal bleeding.

Further assessment

The differential diagnosis of hypermobile joints includes osteogenesis imperfecta, Marfan's syndrome, joint hypermobility syndrome and pseudoxanthoma elasticum. Here, you may take the Ehlers–Danlos syndrome as an established diagnosis and consider whether the chest and back pain might be associated.

- Ask about the nature of the pain (central tightness, pleuritic, worse with movement), site, onset

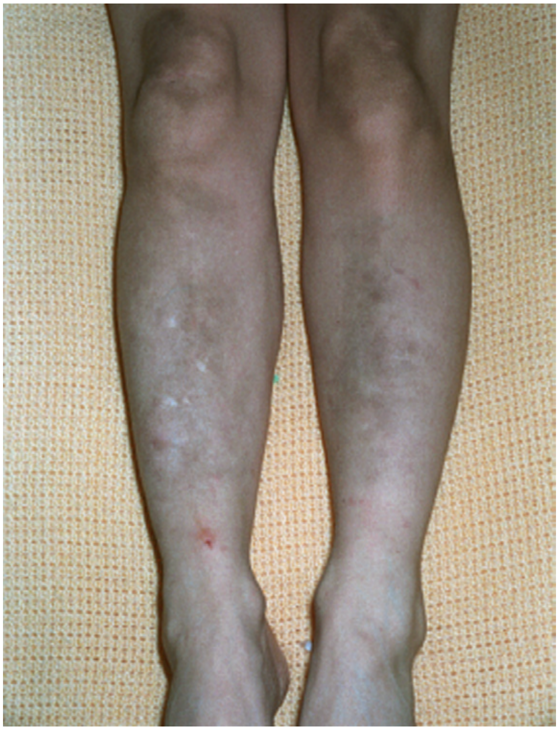


Figure 5.49 Ehlers–Danlos syndrome – skin changes and bruising.

and duration and any precipitating or relieving factors.

- Auscultate the precordium. Potentially serious complications of Ehlers–Danlos syndrome include mitral valve prolapse and aortic dissection.
- Ask about other potential features of Ehlers–Danlos syndrome – myopia, recurrent dislocations and falls.
- Explore concerns.

Feedback to patient

It is not yet clear what the cause of the chest and back pain was. However, we always consider the more serious of possibilities first of all and attempt to exclude these. One uncommon but important association with Ehlers–Danlos syndrome is called aortic dissection, which refers to a tear in the aorta or large blood vessel exiting the heart. We should attempt to exclude this as soon as possible with a chest X-ray and scan of the chest. It could also be that you have fractured a vertebra in the back and we should look for that on X-rays, too, and then consider treatment. With respect to your falls it will be important when you are a little better to consider further input from the orthopaedic team of physiotherapists and occupational therapists. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has skin 'stretchiness', joint hypermobility and kyphoscoliosis.

Provide a diagnosis or differential diagnosis with supporting evidence

He has Ehlers–Danlos syndrome. Aortic dissection must be considered as a cause of back pain although he looks well now after analgesia and the pain is probably musculoskeletal in origin – a vertebral compression fracture should be considered, and his kyphoscoliosis might be contributory. Cardiac pain and pain from pulmonary emboli should always be considered, but I suspect these unlikely.

Outline an investigation and management plan

X-rays of chest and thoracolumbar spine (and possibly scans) and an electrocardiogram are essential and management will depend upon cause.

CASE 5.20 OSTEOGENESIS IMPERFECTA

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Mr James Fulton, aged 40 years

This man has been admitted to the acute medical unit with acute back pain.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 40-year-old man with known osteogenesis imperfecta of moderate severity with previous finger fractures. You developed severe back pain this afternoon whilst gardening and have been admitted to the hospital. You are not taking any medications.

Focused history and examination

Initial history

- Ask about past medical history and confirm osteogenesis imperfecta.
- Establish whether he takes any treatment for bone protection.

Initial examination

- Look for a *blue tinge* to the *sclera* (Fig. 5.50).
- There may be multiple finger *deformities* consistent with previous fractures.

The most commonly used classification for osteogenesis imperfecta is that of Sillence, modified by Glorieux (Table 5.39). In most cases, the underlying genetic abnormality is in genes encoding type 1 collagen (*COL1A1* and *COL1A2*). Several hundred mutations have been described and none is common.

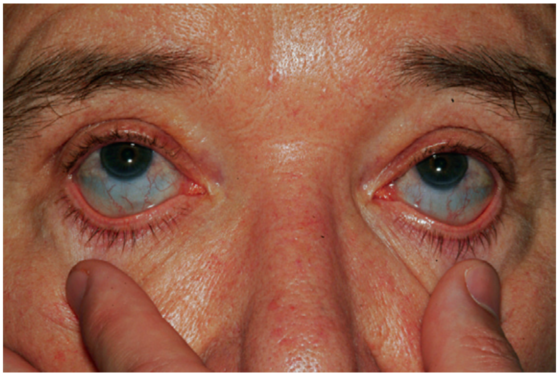


Figure 5.50 Osteogenesis imperfecta – blue sclera.

Table 5.39 Types of osteogenesis imperfecta

Type	Severity	Features
I	Mild	Blue sclera, lightening with age Minimal bowing of long bones Dentinogenesis imperfecta may be present
II	Lethal	Blue sclera. Severe fractures
III	Very severe	Blue sclera. Triangular face, ocular prominence Fractures *in utero*, limbs bowed at birth Dentinogenesis imperfecta
IV	Moderate	Frequent fractures, including vertebral, some deformation
V	Moderate/severe	Progressive deformation, hypertrophic callus formation
VI	Severe	Progressive deformation; growth retardation
Newly identified types are being discovered		

Further assessment

- A likely problem is a vertebral fracture causing the acute back pain.
- Also look at the long bones for deformities and the teeth for dentinogenesis imperfecta with variably coloured, somewhat translucent teeth. Patients with dentinogenesis imperfecta may have accelerated dental caries and are at increased risk of basilar invagination, where the odontoid peg indents the brainstem. Ligament laxity also affects many patients.
- Explore any concerns.

Feedback to patient

Given the increased risk of bone fractures in osteogenesis imperfecta, and given the sudden back pain, I think we must consider the possibility of a fractured vertebra. Firstly we should get you some pain relief for the back pain, either tablets or injection if needed, and obtain some X-rays of the spine. If there is a fracture then it is most likely to heal without any interventional treatment or surgery, and there are various treatments to help protect the bones from recurrent fractures in the future. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has blue-tinged sclera and multiple bony deformities.

Provide a diagnosis or differential diagnosis with supporting evidence

He has osteogenesis imperfecta and may now have had an acute vertebral compression fracture.

Outline an investigation and management plan

Spinal radiology can confirm a fracture. Radiology is also helpful in osteogenesis imperfecta to document the degree of limb deformity and any skull appearances that precede basilar invagination. Management of osteogenesis imperfecta is multidisciplinary – medical therapy centres on bisphosphonates, surgery helps limb deformity, physiotherapy increases muscle strength and stability, occupational therapy selects aids and optimises fine motor skills, orthotics may be needed and pain may be chronic and unremitting and require specialist pain management.

Eye problems

EXAMINATION OF THE EYES

Introduction

The eye has two separate visual faculties, served by different parts of the retina:

- Central vision is served by the central retina, dominated by the macula and a super-specialised area of the macula called the fovea.
- Peripheral vision is served by the peripheral retina.

Unlike a camera photographing images in which everything is reproduced with the same detail, the eye fixes on objects using the central retina and everything in the periphery is appreciated in less detail. Whilst central and peripheral visions appear to merge imperceptibly, the retina's functions are discrete. This is why it is possible to lose central vision and preserve peripheral vision and vice versa.

Central image perception is dominated by the cone photoreceptors in the fovea, particularly sensitive to colour. Peripheral images are perceived by rods, which are particularly sensitive in the dark.

The retina comprises an inner layer of photoreceptors, the neuroretina adjacent to the vitreous, and an outer layer of pigment, the pigment retina, which receives its blood supply from the vascular choroid beneath (Fig. 5.51).

A normal eye brings parallel rays of light to a focus on the retina. Conventionally, beyond 6 m is infinity. Normal distance vision or visual acuity (VA) is said to be 6/6 – meaning that the eye sees at 6 m what it should see at 6 m. 6/24 means it sees only at 6 m what it should be able to see at 24 m. Near vision (< 6 m) is made possible by contraction of the ciliary muscle and alteration in the shape of the lens to shorten the focal length. This is necessary because rays of light entering the eye have diverged slightly from the parallel, and without refractive adjustment by the lens would converge to a focal point beyond the retina (too long a focal length). Long sight occurs when the focal length is too long for the eye. In other words, the eye is too short. Short sight occurs when the focal length is too short for the eye. In other words, the eye is too long. Long- and short-sightedness are merely refractive errors.

Fundoscopy

Neuro-ophthalmological disorders are discussed elsewhere; here the focus is on fundal abnormalities. The retina is the only part of the body where blood vessels and nervous tissue are visualised directly. Fundoscopy (Fig. 5.52) is ideally performed in a darkened room with dilating drops. Examiners appreciate the limits of fundoscopy and PACES abnormalities are likely to be overt.

Approach

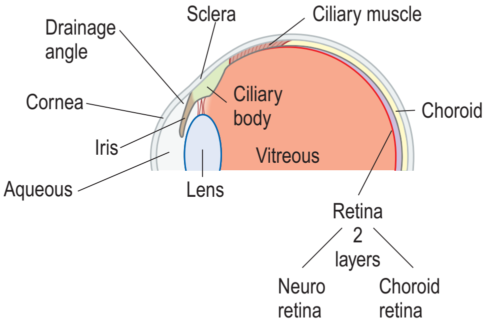
- Approach your patient's right eye from the right side, holding the ophthalmoscope in your right hand, and vice versa for the left eye (Fig. 5.52).
- Ask the patient to gaze on a distant object straight ahead at eye level.

Red reflex

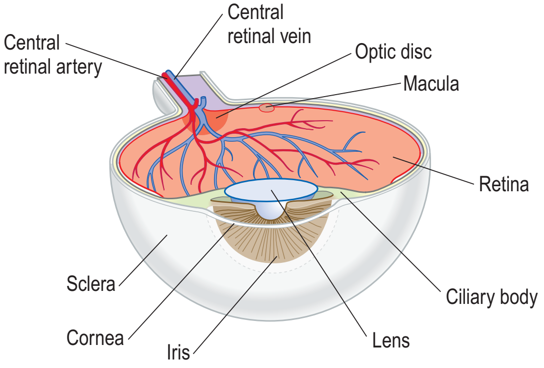
- Check the red reflex. This is attenuated or lost in any condition affecting the transparency of structures in front of the retina (such as a cataract or vitreous haemorrhage), and in any condition affecting apposition of the normally transparent retina with the underlying red vascular choroid (such as retinal detachment).

Anterior structures

- Hold the patient's upper eyelid against the orbit (not against the eyeball!) and approach from 30° to the



Vertical section through the eye



Horizontal section of the left eye, showing relative positions of the pupil, macula and optic disc

Figure 5.51 Anatomy of the eye.

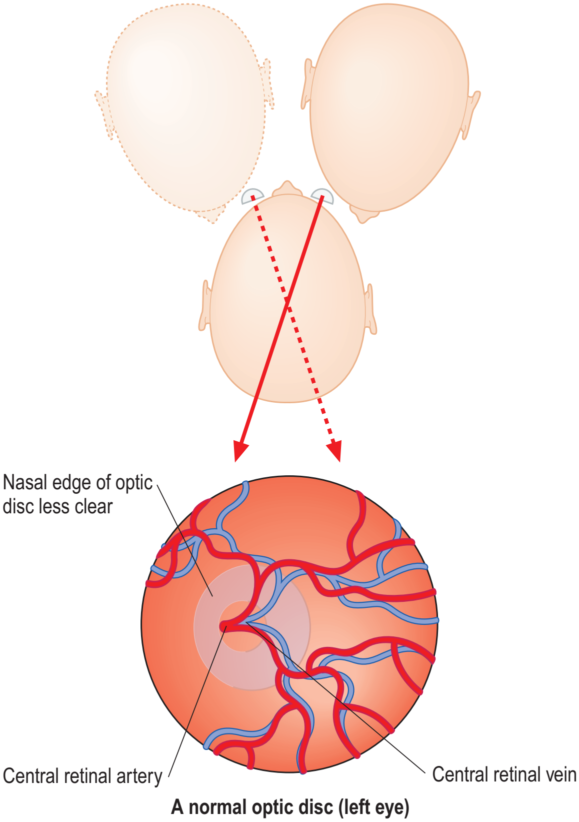

Nasal edge of optic disc less clear
Central retinal artery
Central retinal vein
A normal optic disc (left eye)

Figure 5.52 Fundoscopy.

temporal side. This should ultimately bring the optic disc straight into view. Tilting your head sideways gives both the patient and yourself 'breathing space' and enables you to get close to the patient's eye. The closer you are, the easier it is to angle your ophthalmoscope into each quadrant and the bigger your field of view of the fundus.

- Before looking at the optic disc, focus through the anterior chamber, lens and vitreous as you proceed. Find '0' on the ophthalmoscope. West of '0' are negative numbers and east of '0' positive numbers. Dial clockwise so that you start with a short focal length focusing on the cornea. Dialling progressively anticlockwise, through progressively longer focal lengths, will focus through the anterior chamber, lens (detecting any cataract), vitreous and finally onto the fundus. This takes practice. Remember that short-sighted people have long eyes and '0' will focus on the vitreous; long-sighted people have short eyes and '0' will come to a focus behind the eye; if a patient is wearing their glasses then '0' will come to a focus on the retina.

Box 5.23 **Some normal appearances of the optic disc**

The nasal margin of the disc is normally less sharply demarcated than the temporal margin, and a rim of pigment seen on the temporal margin is very common. 'Early papilloedema' and 'retinitis pigmentosa' are often suggested apprehensively by candidates hoping to have seen more overt signs!

The centre of the optic disc is normally paler than the rim, and the vessels are seen to plunge into it. The colour of the optic disc varies in adults. Where only the four main vessels are seen on the disc it is normally quite pale. Where the vessels have early branches on the disc itself it appears much pinker. Sometimes elderly patients have very pale discs because of thin vessels.

Optic disc

- Now examine the optic disc. This full moon-like circle is the optic nerve's head. Note its *margin*, *cup* and *colour*. If only blood vessels come into immediate view, follow them backwards against the angles of their branches. This should bring the optic disc into view.
- Be aware of some normal appearances of the optic disc, which confuse many candidates (Box 5.23).

Blood vessels

- Next pursue the four major vessels into each quadrant.

Macula

- Remember to look temporally at the macula. This can be done by asking your patient to look directly at the light. The *macula* is found two disc diameters from the temporal margin of the disc and appears as a pale yellow spot on a slightly darkened area of retina. It can be difficult to see (Box 5.24).

Summary

A summary of the fundoscopy examination sequence is in the Summary box.

SUMMARY BOX – FUNDOSCOPY EXAMINATION SEQUENCE

- ◆ Check for the red reflex and look for cataracts.
- ◆ Look at the optic disc and be aware of normal variants.
- ◆ Follow the blood vessels into each quadrant, noting any abnormalities.
- ◆ Look at the macula.

Box 5.24 Macula, optic disc, central scotoma and blind spot

Candidates get very confused about the *macula*, the *optic disc* (the optic nerve's head), *central scotomas* and *blind spots*. What especially confuses (and is seldom explained in books) is how disease either at the macula or at the optic disc can produce a central scotoma.

The retina comprises a nerve cell (photoreceptor) layer and a deeper pigment layer, its pigment layer lying over the highly vascular choroid. The nerve fibres from the photoreceptors run in an orderly fashion to the optic disc (where they become tightly packed, their millions of converging axons giving rise to the disc's pale appearance) and become the optic nerve. The most important area of the retina is the macula, an area crowded with photoreceptors, whose axons form the most important bundle of fibres entering the optic nerve, the *papillomacular bundle*.

The optic disc, although an area of densely packed nerve fibres, is an area of retina without photoreceptors to receive visual images. The optic disc 'cannot see' and its corresponding visual axis is termed the blind spot (Fig. 5.53). The macula, on the other hand, is an area of densely packed photoreceptors (the fovea being its centre of excellence) and its corresponding visual axis is the area of central vision. Lesions of the macula therefore classically result in a central scotoma (Fig. 5.53).

Sometimes it is not just the macula that is damaged but a wider area of receptors and axons situated between the macula and the optic disc. In such cases the scotoma is large, extending between the visual axes of the macula and the optic disc, and this is called a caecocentral scotoma.

Optic atrophy implies damage to and degeneration of axons entering the optic disc. Because the papillomacular fibres are densely packed and thus vulnerable to a heavy casualty rate, central vision disturbance is marked, and can even result in a central scotoma or caecocentral scotoma.

In the early stages of optic disc swelling (Case 5.23) there is no visual disturbance. Later, retinal oedema may cause blind spot enlargement. Haemorrhages or oedema extending to the macula may cause abrupt central vision disturbance. Chronic scarring resulting from optic disc swelling may cause secondary optic atrophy with a central scotoma and / or progressive visual field restriction as fibres from the periphery entering the optic disc also degenerate.

Arcuate scotomas result from a wide variety of lesions. Arcuate scotomas are scotomas corresponding to damage to a bundle of nerve fibres entering the optic nerve. Primary open-angle glaucoma causes a special type of arcuate scotoma that radiates from the blind spot. This is because raised intraocular pressure damages nerve fibres at the disc margins.

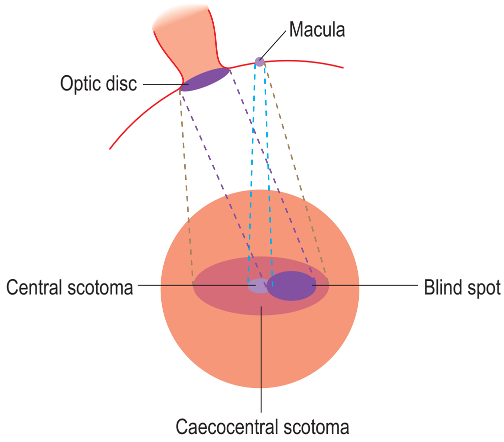


Figure 5.53 The optic disc, the macula, the blind spot and central scotomas.

Cases

CASE 5.21 DIABETIC RETINOPATHY

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Zoe Jackson, aged 35 years

This woman is in hospital for treatment of cellulitis and unstable blood sugars. She asks if you might check on her chronic eye condition.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old woman in hospital for an unrelated problem but you have diabetes and background diabetic retinopathy and ask if the doctor might check on this as you missed your last screening appointment. You have poor glycaemic control, having a busy family and not always being concordant with your insulin regimen. You are also currently 3 months pregnant.

Focused history and examination

Initial history

- Ask about the visual symptoms (visual acuity and any loss) and any previous treatment.

- Ask about the level of diabetes control and current medication.
- Ask whether there are other known diabetes complications – neuropathy (peripheral neuropathy, mononeuropathy/femoral neuropathy), nephropathy and macrovascular complications, e.g. ischaemic heart disease, stroke.

Initial examination

- Perform fundoscopy.

Diabetic retinopathy (DR) is a microvascular process in which high retinal blood flow induces microangiopathy in capillaries, arterioles and venules, causing vessel occlusion and leakage of plasma contents into the retina itself. DR may be staged separately from diabetic maculopathy, and may be non-proliferative diabetic retinopathy (NPDR), which includes background diabetic retinopathy (BDR) and preproliferative diabetic retinopathy (PPDR), proliferative diabetic retinopathy (PDR) or advanced eye disease.

Background diabetic retinopathy (BDR)

There are *microaneurysms (dots)*, *hard exudates* and *'dot and blot' haemorrhages* (Box 5.25 and Fig. 5.54).

Preproliferative diabetic retinopathy (PPDR)

There are, in addition to background changes, *cotton wool spots* (Box 5.26, Fig. 5.55) and larger blot or 'blotch' haemorrhages. There is *dilatation and beading of retinal veins* (sausage appearance).

BDR and PPDR are now often replaced by the term NPDR, classified in Box 5.27.

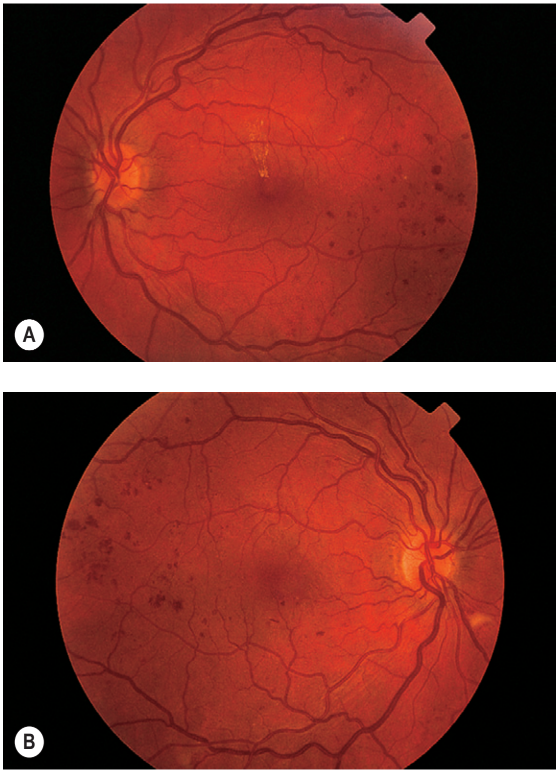


Figure 5.54 (A, B) Microaneurysms, hard exudates and blot haemorrhages. Note that the hard exudates are close to the macula and that the haemorrhages are of different sizes. Sometimes it is difficult to differentiate between smaller 'blot' and larger 'blotch' haemorrhages.

Box 5.25 **Background diabetic retinopathy**

Microaneurysms

These are bulges in weakened vessel walls and appear as red dots scattered throughout the fundus, but most commonly temporal to the macula. They arise as a direct result of capillary occlusion.

Hard (leakage) exudates

These are discrete yellow protein–lipid-rich deposits. They represent lipid which has leaked from vessels and been engulfed by macrophages. They commonly occur at the edges of microvascular leakage and may form a circinate pattern around a leaking microaneurysm. They may coalesce to form sheets.

Haemorrhages (dot blot)

Haemorrhages from microaneurysms and weakened vessels appear red but their shape depends upon their site. Deep haemorrhages are round (blots) because they are confined by the tightly packed layers of the deep retina. Superficial haemorrhages are larger and blotchy because they follow the pattern of nerve fibres.

Box 5.26 **Preproliferative retinopathy**

Cotton wool spots

These indicate ischaemic axons within the retina. They arise because of arteriolar occlusion.

Venous dilatation and changes

Venous dilatation is a sign that retinal blood supply is trying to keep up with demand and venous beading results from sites of complete vessel closure. Venous loops and sausage segmentation also occur.

Intraretinal microvascular abnormalities

The term intraretinal microvascular abnormalities refers to dilated capillaries. Microaneurysms and intraretinal microvascular abnormalities are best seen as black dots and lines against a green background when the ophthalmoscope's green filter is used to eliminate the redness of the choroid.

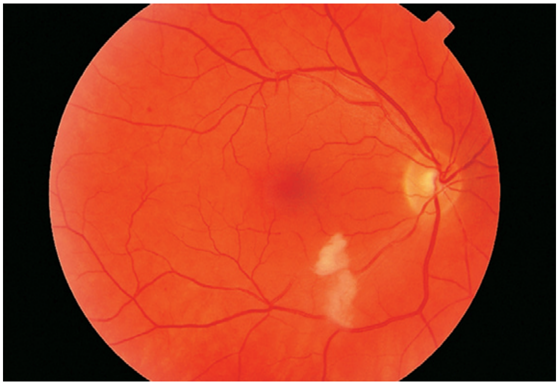


Figure 5.55 Cotton wool spot. Note also the small blot haemorrhage at 11 o'clock.

Box 5.27 **Non-proliferative diabetic retinopathy**

- Mild – microaneurysms
- Moderate – four blots in one quadrant and / or cotton wool spots or venous beading or intraretinal microvascular abnormalities
- Severe – severe haemorrhage in four quadrants or venous beading in two quadrants or severe intraretinal microvascular abnormalities in one quadrant
- Very severe – any two of severe

Box 5.28 **Neovascularisation**

Neovascularisation occurs in response to occlusive ischaemia (which stimulates angiogenic factors) and affects veins, not arteries. New vessels are usually 'wild' in appearance. They tend to loop off veins and can look like fronds of seaweed.

Proliferative diabetic retinopathy (PDR)

There is, in addition to NPDR changes, *neovascularisation* (Box 5.28, Fig. 5.56). There may be extensive *laser photocoagulation therapy scarring* (Fig. 5.57).

Advanced eye disease – retinal haemorrhage and retinal detachment

There is, in combination with any of the above features, *preretinal* or *vitreous haemorrhage* and / or (tractional) *retinal detachment* and / or *rubeosis iridis* (Box 5.29, Fig. 5.58).

Diabetic maculopathy

There is evidence of diabetic eye disease near the macula (Box 5.30). This usually takes the form of *hard exudates* (tending to form *circinate rings*) and *oedema* (Fig. 5.59). There may be *neovascularisation*.

Further assessment

Diabetic eye disease is usually easy to recognise, the main dilemma being to differentiate it from hypertensive

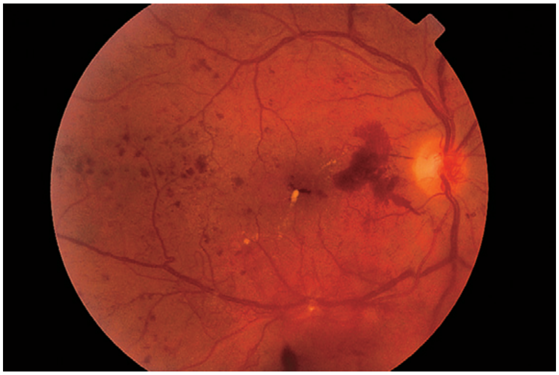


Figure 5.56 Diabetic retinopathy changes throughout the fundus with neovascularisation at the optic disc. Neovascularisation is also seen notably at 7 o'clock and 11 o'clock (where new vessels have tended to form loops). Note also the large haemorrhage between the optic disc and the macula.

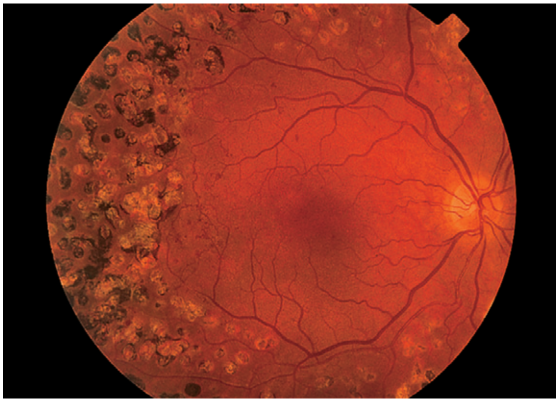


Figure 5.57 Photocoagulation scars. Note neovascularisation at 8 o'clock.

Box 5.29 **Advanced eye disease**

Subhyaloid haemorrhages are retained by the hyaloid membrane but may blow into the vitreous, threatening vision completely in the affected eye because they are then restrained only by the limits of the vitreous cavity. Retinal detachment can occur when new vessels exert traction on the retina. Rubeosis iridis (new vessels on the iris) may lead to rubeotic glaucoma.

Box 5.30 **Maculopathy**

There are three types:

- Focal exudative – hard exudates within 500 μm of the fovea if associated with retinal thickening
- Retinal oedema – within 500 μm (one-third of a disc diameter) of the fovea or one disc diameter or larger, any part of which is within one disc diameter of the fovea
- Ischaemic maculopathy.

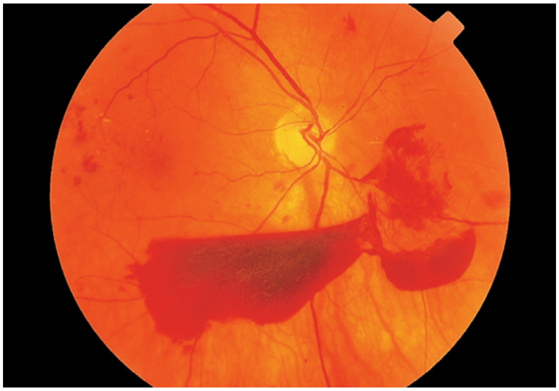


Figure 5.58 Subhyaloid (preretinal) haemorrhage in diabetic retinopathy. Blood is in the posterior vitreous space and tends to settle inferiorly and outline the attachment of the vitreous to the retina. The appearance has been likened to a bird's nest. A subhyaloid haemorrhage may also be seen with a subarachnoid haemorrhage. Note how a subhyaloid haemorrhage obscures retinal vessels (compare with a choroidal haemorrhage in Fig. 5.74).

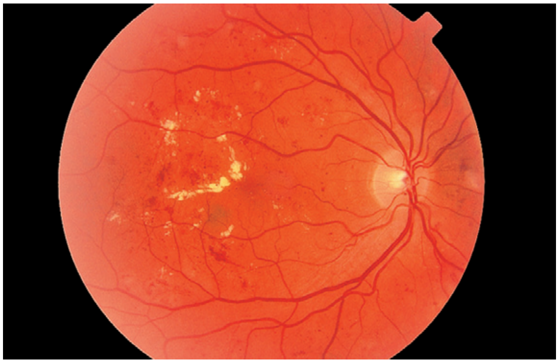


Figure 5.59 Hard exudates forming a circinate ring at the macula. Note how bright and crisp leaking exudates are compared with cotton wool spots. Note also haemorrhages of varying size.

retinopathy. Microaneurysms are almost pathognomonic of diabetes, but may occur in venous occlusion. They must be present to diagnose diabetic retinopathy. This said, general physicians cannot possibly be aware of the vast array of retinal and other eye diseases that are the preserve of ophthalmologists. Cotton wool spots, for example, usually in the superior pole and lasting around 6 weeks but changing over time, have the same appearance regardless of the wide range of underlying causes, which include diabetes, hypertension, lupus, vasculitis, heavy smoking, anterior ischaemic optic neuropathy and human immunodeficiency virus infection. Haemorrhagic retinopathy has causes as disparate as Behçet's disease, tuberculosis and leukaemia, and viral infections like herpes simplex, herpes zoster and cytomegalovirus, which can cause acute retinal necrosis.

- Be aware of non-retinal eye complications that may occur in diabetes mellitus – cataracts (early onset age-related or snowflake cataracts in poorly controlled type 1 diabetes) or visual changes caused by osmotic alteration in lens shape, ocular nerve palsies (especially a sixth-nerve palsy), increased risk of infection (conjunctivitis, styes, herpes zoster, hypopyon – also in HLA-B27-related disorders, Behçet's disease and leukaemias) and central retinal artery and vein occlusion.
- Explore the issues around her concordance with treatment.

Feedback to patient

I think this is still background diabetic retinopathy, but digital photography through the diabetic screening service is important to be sure of this. We can make sure, before you are discharged from hospital, that an appointment is arranged. I appreciate the reasons for your erratic insulin taking, but I think it very important that we arrange further review by the diabetes team before you go home. Good control of diabetes is vital for three reasons here:

Firstly, the level of diabetic control (HbA_{1c}) is associated with the likelihood of eye as well as other complications including the infection that brought you into hospital.

Secondly, rapid worsening of eye disease may occur in pregnancy.

Thirdly, worsening retinopathy may occur with rapid tightening of glycaemic control.

I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

There are microaneurysms, hard exudates and small dot haemorrhages in both eyes.

Provide a diagnosis or differential diagnosis with supporting evidence

This is probably still background diabetic retinopathy, but for reasons mentioned (poor control, pregnancy, sepsis) it is very important to involve the diabetes team urgently and obtain formal screening soon.

Outline an investigation and management plan

Diabetic eye disease is the commonest cause of blindness in the UK for patients of working age. Two per cent of the UK population have diabetes, 10–13% of whom have sight-threatening retinopathy. Type 1 diabetes patients generally have 5–10 years of disease before developing eye signs but eventually nearly all succumb. Type 2 diabetes patients may have eye signs at diagnosis and are more prone to maculopathy.

Risk factors for diabetic retinopathy include disease duration, poor glycaemic control, pregnancy, hypertension and nephropathy.

Box 5.31 Management of diabetic retinopathy

- Non-proliferative diabetic retinopathy (NPDR) with microaneurysms alone requires annual screening with good overall diabetic control. All other grades of NPDR warrant ophthalmological referral (non-urgently except for very severe). In addition to strict diabetic control, a decision must be made about prophylactic laser photocoagulation therapy.
- Proliferative diabetic retinopathy (PDR) and advanced eye disease require urgent ophthalmological referral for laser photocoagulation therapy. Panretinal photocoagulation (scatter laser treatment) is used to create hundreds or thousands of tiny burns to the retina which aims to destroy ineloquent areas of retina (not concerned with vision) and thus attenuate synthesis of angiogenic factors. In advanced PDR burns are used to destroy abnormal blood vessels and can reduce the risk of severe vision loss by 50%. Patients may lose some peripheral, colour and night vision.
- Vitreous haemorrhage requires urgent referral and can be treated with vitrectomy.
- Maculopathy requires ophthalmological referral. Focal laser therapy may be indicated but must be balanced against potential risk to eloquent tissue. Intravitreal triamcinolone acetonide decreases macular oedema and is very effective but the effect is transient, lasting up to 3 months, necessitating repeated injections. Complications include cataract, glaucoma and endophthalmitis.
- Other treatments are now becoming available, e.g. kinase inhibitors and anti-vascular endothelial growth factor. Avoiding smoking and treating hypertension are very important.

Screening with digital retinal photography and appropriate management [Box 5.31] has been shown to prevent blindness in 80% of patients with proliferative diabetic retinopathy and 50–60% of patients with maculopathy. Routine screening of all diabetic patients is mandatory at least annually.

CASE 5.22 HYPERTENSIVE RETINOPATHY

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Paul Richards, aged 56 years

This man is in hospital with a hypertensive crisis. As part of your assessment for target organ damage you are keen to check his eyes.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

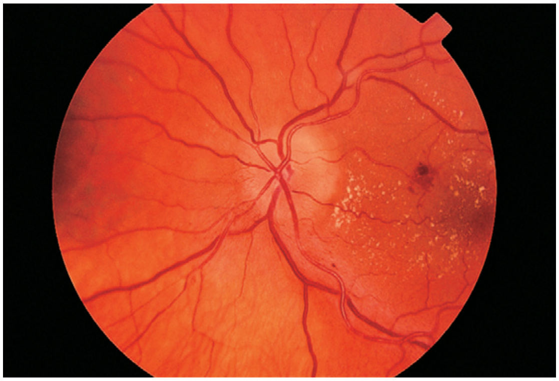


Figure 5.60 Hypertensive retinopathy. Note arteriovenous nipping, the 'wire' appearance of some vessels, leakage (hard) exudates, haemorrhages and blurring of the optic disc margin.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 56-year-old man in hospital following an episode of severe hypertension. You are known to have a chronic kidney condition. You have not been concordant with antihypertensive medication because of side effects (ankle swelling and headaches from a non-rate-limiting calcium channel antagonist). You cannot recall the names of the other tablets you have tried in the past. The doctor wishes to assess your eyes for evidence of hypertensive damage.

Focused history and examination

Initial history

- Ask about any visual symptoms including visual loss.
- Ask about the chronic kidney condition and other past medical history. Be aware of the widespread manifestations of hypertension – cardiovascular disease, cerebrovascular disease, renovascular disease and peripheral vascular disease.
- Ask about medication.

Initial examination

- Perform fundoscopy.

Hypertensive retinopathy may progress through a number of stages:

- *Focal arteriolar attenuation and arteriovenous (AV) nipping* represent the presence of arteriosclerosis of any cause. Thickened arteriolar walls appear like '*silver*' or '*copper*' wires (Fig. 5.60).
- Narrowing of arterioles leads to localised areas of infarction of the superficial retina (*cotton wool spots*)

Box 5.32 **Understanding the signs in hypertensive retinopathy**

- In childhood, retinal arterioles and venules are of equal width, highly elastic and glisten in the light of an ophthalmoscope. Even normotensive adults lose the sparkling retinal appearances of youth. But hypertension slowly replaces the elastic tissue with fibrous tissue and the glistening disappears. The muscular layer of arterioles is often also replaced and these become rigid. Any remaining arteriolar muscle, still capable of contraction, can give rise to the appearance of *focal arteriolar attenuation*, as the fibrosed segments maintain a static calibre or even dilate.
- *Silver wiring* is an unreliable sign, but *arteriovenous nipping* is the natural progression of arteriolar calibre change and the best sign of arteriosclerosis of any cause. It occurs at sites where dilated arterioles cross over or under venules. The 'compression' or 'nipping' is an illusion.
- *Flame-shaped haemorrhages* occur in the surface layers of the retina (similar to large diabetic haemorrhages) and *hard exudates* are common at the macula, threatening central vision. They often appear as a *star*, following the line of retinal fibres around the macula.
- *Cotton wool spots*, as for diabetes, indicate ischaemia. They may also be a feature of vasculitis, cholesterol emboli, bacterial endocarditis and myeloproliferative disease.
- *Swelling of the optic disc* implies accelerated hypertension.

and *flame-shaped haemorrhages*. Leakages from these vessels result in *hard exudates* (Fig. 5.60).

- *Optic disc swelling*, along with cotton wool spots, flame-shaped haemorrhages and hard exudates, indicates what has been termed '*malignant hypertension*'. Although defined by disc swelling rather than an absolute blood pressure measurement, blood pressure is often above 200/140 mmHg. *Accelerated hypertension* refers to a recent increase over previous hypertensive levels associated with vascular damage on fundoscopy but without disc swelling. Beware of diagnosing hypertensive retinopathy if disc swelling is unilateral or if it occurs in the absence of other signs of hypertensive retinopathy.

These signs are explained in Box 5.32.

Additionally, both central retinal artery and central retinal vein occlusion may occur in hypertension with or without hypertensive retinopathy.

Further assessment

- Explore the issues around his concordance with treatment.

Feedback to patient

There appears to be some evidence that the high blood pressure has affected the backs of the eyes. Blood vessels supplying the retina are subject to pressure effects as with any other blood vessels in the body. It would be advisable for us to obtain digital photographs of each retina as a baseline for comparison in the future, and the best solution to preventing future damage is to control blood pressure rigorously, in collaboration with your kidney specialist. It is going to be very important in future to do all we can to keep the blood pressure well controlled and there are plenty of alternative medications which will not cause you to have headaches or ankle swelling. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

There is, in both eyes, the presence of focal arteriolar attenuation and arteriovenous nipping, cotton wool spots and flame-shaped haemorrhages, and hard exudates

Provide a diagnosis or differential diagnosis with supporting evidence

This is hypertensive retinopathy.

Outline an investigation and management plan

It may be that he has chronic kidney disease from a primary kidney condition with secondary hypertension, or it may be that his chronic kidney disease is driven by hypertension and renovascular disease, or it may be a combination of both. Whichever way, I would gather information from his renal specialist to determine whether further investigations are warranted and which antihypertensive agents might now be considered. Depending upon the severity of his chronic kidney disease and any prior exposure, attempts to block the angiotensin system might be valid.

CASE 5.23 SWOLLEN OPTIC DISC AND PAPILLOEDEMA

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Sarah Dunne, aged 35 years

This woman is in hospital with headaches. As part of your assessment you are keen to check her eyes.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old woman in hospital for investigation of headaches. This has been a problem for a few months. You are usually well but your own doctor has been concerned that you are overweight. You take the combined oral contraceptive pill. The doctor wishes to assess your eyes. You are anxious to get home as soon as possible because you have young children.

Focused history and examination

Initial history

- Ask about any visual symptoms including visual loss.
- Ask about any past medical history.
- Ask about medication.

Initial examination

- Perform fundoscopy.

There are many causes of optic disc swelling. Papilloedema, by definition, is swelling of the optic disc due to raised intracranial/cerebrospinal fluid pressure. This should be distinguished from other causes of disc swelling. A sequence of optic disc signs results from evolving optic disc swelling:

- The veins become dilated and tortuous and capillary dilatation leads to hyperaemia of the disc.
- The centre of the disc (the *cup*), becomes *pinker than normal* and *less distinct* as it swells. The *vessels seem to disappear* suddenly in the oedema before reaching the cup. The *disc margins blur* (Fig. 5.61) as the nerve fibre layers swell.
- The entire disc eventually becomes swollen and raised and the origins of vessels completely disappear. At this stage (Fig. 5.62), retinal *haemorrhages*, *exudates* and *cotton wool spots* may also appear, although any haemorrhages are never as dramatic as in central retinal vein occlusion. *Loss of venous pulsation* implies raised intracranial pressure and is a feature of *papilloedema*. It is difficult to detect and is a normal finding in many individuals. However, *spontaneous venous pulsation excludes papilloedema*.

The pathophysiology of papilloedema remains obscure but involves transmission of elevated cerebrospinal fluid pressure along the optic nerve sheath, followed by impaired venous drainage from the eye. Papilloedema may take weeks or months to develop, and is therefore a late sign of raised intracranial pressure. Papilloedema may be detected in its early stages by fluorescein angiography.

Further assessment

- Check for enlargement of the blind spot by visual field testing. Unless there is also pathology in the optic nerve itself, the visual fields should otherwise be normal. Chronic untreated hypertension may result in macular oedema (with macula stars), which can rapidly disturb central vision.
- Consider the causes of optic disc swelling (Box 5.33); see also Fig. 5.63.
- Explore concerns.

Feedback to patient

There appears to be some evidence that high fluid pressure has affected the backs of the eyes. With the headaches it may be that you have a condition called idiopathic intracranial hypertension in which there is a problem with drainage of fluid around the brain. But we do need to consider other possibilities as well, and I would think that a scan of the brain is sensible in the first instance. I'd be happy to answer any questions you may have, although it will be important to understand exactly what is wrong quickly so that we are in a better position to advise you about what to do, and of course get you home without delay. Idiopathic intracranial hypertension, for example, is a condition treatable by removing some spinal fluid.

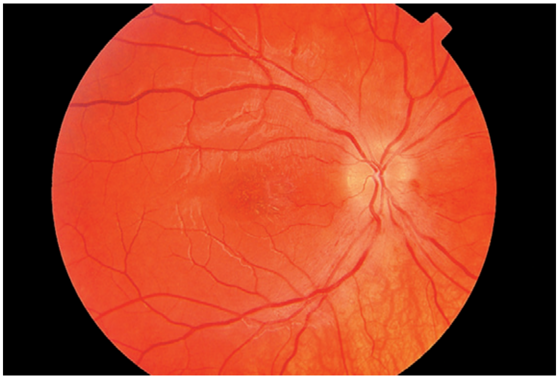


Figure 5.61 Swollen optic disc (blurring of disc margins).

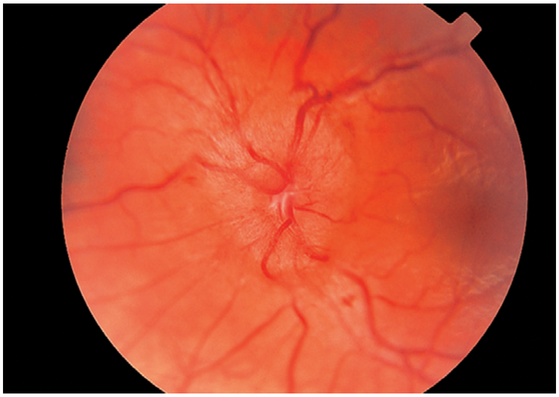


Figure 5.62 Swollen optic disc (more advanced case).

Box 5.33 **Causes of optic disc swelling**

- Papilloedema (beware unilateral papilloedema*)
- Accelerated hypertension
- Optic papillitis
- Ischaemic optic neuropathy
- Hypercapnia
- Central retinal vein occlusion
- Hyperproteinaemic disorders, e.g. Waldenström's macroglobulinaemia
- Pseudopapilloedema**

*Papilloedema may be due to any cause of raised intracranial pressure and so bilateral papilloedema can occur with space-occupying lesions; however, unilateral papilloedema should always raise concern about space occupation and Foster–Kennedy syndrome refers to optic atrophy caused by compression of one optic nerve by an intracranial mass, together with contralateral papilloedema due to raised intracranial pressure.

**This is not papilloedema. It occurs in a small, long-sighted and often astigmatic eye where the optic disc appears to be crowded by other structures. Apart from the refractive error, there should be no abnormalities, but doubt can be resolved by fluorescein angiography. Pseudopapilloedema can also result if a disc is raised by drusen.

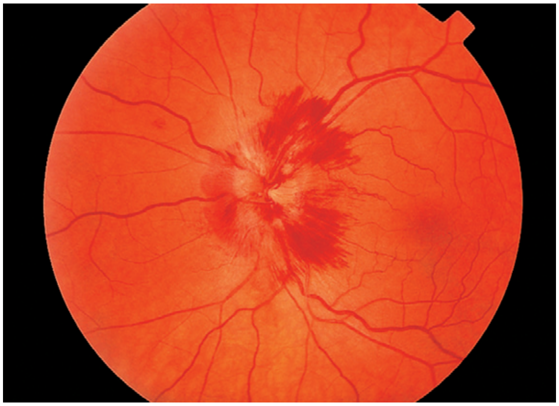


Figure 5.63 Swollen optic disc. Note the fiery red burst emanating from the optic disc, often seen in retinal vein thrombosis.

Feedback to examiners

Summarise the key history and examination findings

This woman has headaches and bilateral papilloedema.

Provide a diagnosis or differential diagnosis with supporting evidence

She probably has idiopathic intracranial hypertension. She could conceivably have a space-occupying lesion. Other causes of optic disc swelling include accelerated hypertension and central retinal vein occlusion, although she has no signs of the latter.

Outline an investigation and management plan

Brain imaging is necessary in the first instance to exclude a space-occupying lesion. Idiopathic intracranial hypertension is possibly caused by microthrombi compromising dural venous drainage, although the cause is not really clear. The condition usually affects young to middle-aged females and has been associated with the oral contraceptive pill and corticosteroids. Raised cerebrospinal fluid pressure is a central feature, causing the papilloedema and headaches, and the condition responds to therapeutic cerebrospinal fluid drainage. A neurologist should be involved in her management.

CASE 5.24 OPTIC ATROPHY

Candidate information

Role

You are a doctor on the neurology ward.

Scenario

Re: Mrs Linda Jones, aged 35 years

This woman is in hospital with an exacerbation of a chronic neurological condition. She has had worsening visual acuity recently.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old woman in hospital with a relapse of multiple sclerosis, presenting initially with transverse myelitis. Your vision has deteriorated recently. You are aware that multiple sclerosis affects the eyes and have asked the doctor to examine your eyes for signs of damage.

Focused history and examination

Initial history

- Ask about the visual loss – central or peripheral, abrupt or insidious.
- Ask about past medical history and the main pattern and complications of the multiple sclerosis (including any previous eye involvement), whilst preparing for fundoscopy.

Initial examination

- Perform fundoscopy. The *optic disc* flashes in to view, *bright*, *white* and *crisp*, like a bright full moon in a dark sky (Fig. 5.64).
- Assess for the five signs of optic nerve damage (Box 5.34).

Optic atrophy is not an all or nothing phenomenon. There are 'shades of white' depending upon the degree of axonal degeneration, and hence degrees of visual disturbance. Patients with multiple sclerosis who have recurrent episodes of optic neuritis develop progressive worsening of the five signs. Episodes of demyelinating optic neuritis (Box 5.35) in multiple sclerosis are by far the commonest cause of optic atrophy in the UK. While a single episode of optic neuritis (without other preceding neurological features) does not necessarily imply multiple sclerosis, a high proportion (up to 75%) of patients will develop other signs of multiple sclerosis over time.

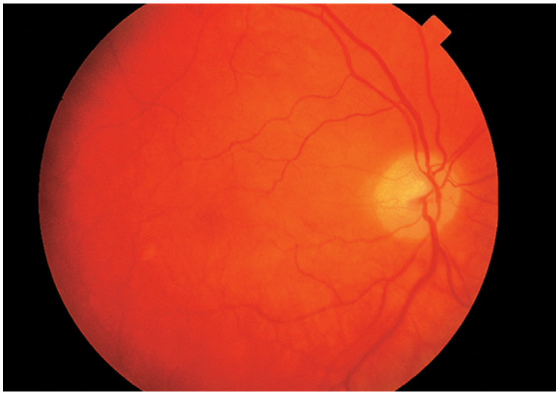


Figure 5.64 Optic atrophy. Note how the optic disc is instantly eye catching.

Box 5.34 **Five signs of optic nerve damage**

1. Relative afferent papillary defect, the most sensitive and specific sign
2. Decreased visual acuity
3. Attenuated colour vision
4. Central or paracentral scotoma
5. Optic atrophy

Box 5.35 **Optic neuritis – papillitis and retrobulbar neuritis**

In papillitis, inflammation is just behind the optic disc, which may be swollen with blurred margins and floridly coloured because of hyperaemia and haemorrhage. In acute retrobulbar neuritis the optic disc appears normal because the inflammation is further back along the optic nerve. Papillitis is usually distinguishable from papilloedema because papilloedema is usually bilateral and does not give rise to the five signs of optic nerve damage.

Further assessment

- Consider the causes of optic atrophy (Table 5.40).
- Explore concerns.

Feedback to patient

> The optic discs – these are the areas in each eye where the optic nerves that carry the signals for vision join onto the retina – do appear to be paler than normal. This can occur if nerve fibres of the optic nerve have been affected by the demyelination

Table 5.40 Causes of optic atrophy

Cause	Description
Demyelinating optic neuritis (retrobulbar neuritis or papillitis)	See text
Ischaemic optic neuritis	Atherosclerotic or vasculitic, notably a complication of untreated giant cell arteritis
Compression	From tumours, aneurysms, glaucoma or Paget's disease
Toxic optic neuritis	From chemicals and drugs such as methanol, tobacco, lead, ethambutol, isoniazid, chloramphenicol and digoxin
Infiltrative lesions	Granulomatous infiltration of the optic nerve in tuberculosis, sarcoidosis or syphilis, or from carcinoma
Infection	Meningitis, encephalitis, neurosyphilis
Neurodegeneration	May occur in vitamin deficiencies (especially B1 and B12), tabes, or hereditary conditions such as Friedreich's ataxia. Leber's hereditary optic neuropathy, a mitochondrial cytopathy, is a rare cause affecting mostly young adult males
Retinitis pigmentosa	This is associated with severe vessel narrowing, which is thought to be the reason for the frequently associated optic atrophy (ischaemic)
Glaucoma	
Secondary (consecutive) optic atrophy	The term consecutive optic atrophy refers to atrophy due to degeneration of parent ganglion cells and may contribute to the disc pallor in retinitis pigmentosa, chorioretinitis and central retinal artery occlusion. It also occurs as a legacy of papilloedema due to scarring (gliosis) in the optic disc. The disc margin is not usually crisp as it is in primary atrophy.

Colobomata may sometimes resemble optic atrophy. These result from persistence of the inferior embryonic cleft of the eyeball, which is present during development. A coloboma appears as a white hole in the retina, or if in the disc itself as a big white patch. Colobomata occasionally extend into the iris. Colobomata may cause central scotomas or arcuate scotomas.

of multiple sclerosis. It will be important to get the advice of the neurologist and in all probability an ophthalmologist on this, as firstly we need to consider how recent or longstanding this process is thought to be, and secondly we should decide what treatment might be best. I'd be happy to talk about any of this in more detail or answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has a history of multiple sclerosis and now has decreased visual acuity and attenuated colour vision with pale optic discs.

Provide a diagnosis or differential diagnosis with supporting evidence

She has bilateral optic atrophy.

Outline an investigation and management plan

Visual loss during each episode of optic neuritis may be subtle, often described as a 'steamed up' sensation and often only noticeable when the good eye is closed. A key associated symptom is pain, especially on eye movement, often preceding visual disturbance. Recovery from an episode of optic neuritis is usual within a few weeks, although, even when the field defect resolves, a defect in sharp colour vision persists. Visual evoked potential testing usually detects delayed conduction consistent with demyelination and neuronal loss. Optic neuritis may be treated with corticosteroids, usually intravenously.

CASE 5.25 RETINITIS PIGMENTOSA AND CHORIORETINITIS

Candidate information

Role

You are a doctor on the stroke unit.

Scenario

Re: Mrs Jane Horsley, aged 70 years

This woman is in hospital with a stroke and your junior doctor colleague has asked you to examine her fundi, which he believes to be abnormal.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old woman in hospital following a stroke with dysphasia. You are progressing well. You have retinitis pigmentosa, which has severely affected your vision, but have been unable to communicate this diagnosis to the doctors on account of your current word-finding difficulty.

Focused history and examination

Initial history

- On discovering the dysphasia, seek permission to examine the eyes.
- Ask whether there is a known eye condition and following examination attempt to confirm this with the patient.

Initial examination

- Perform fundoscopy.

There are webs of *pigment* in the *peripheral retina* (Fig. 5.65).

Further assessment

- Appearances are absolutely characteristic in retinitis pigmentosa, although chorioretinitis can produce pigmentation and pose a trap for the untrained eye; these are entirely separate conditions other than giving rise to retinal pigmentation. In chorioretinitis there is evidence of previous inflammation of the chorioretinal layers. Patches of the normal pink chorioretina are stripped away to reveal the underlying white sclera. Typically, there are *multiple small white and black patches*, the black reflecting proliferation of retinal pigment (Fig. 5.66). Retinitis

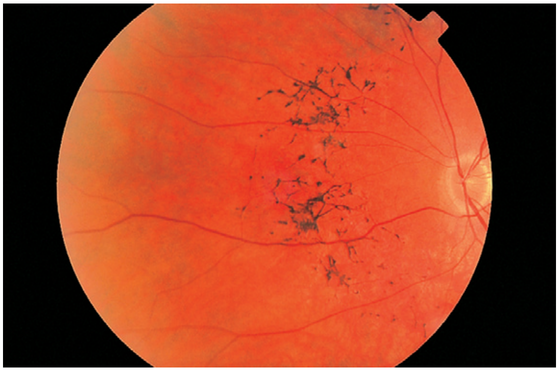


Figure 5.65 Retinitis pigmentosa.

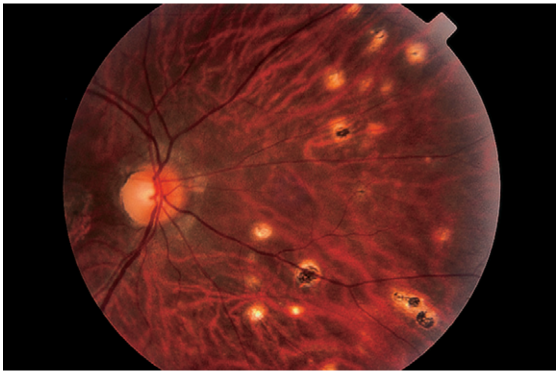


Figure 5.66 Chorioretinitis.

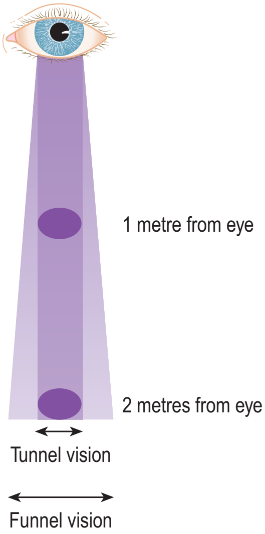


Figure 5.67 Funnel and tunnel vision.

pigmentosa may be associated with optic atrophy, the result of marked narrowing of arterioles and retinal cell ischaemia / loss. Chorioretinitis is often idiopathic, but may be associated with antecedent infection, e.g. *Toxoplasma*. A pigmented retina as a result of normal racial variation or due to pan-retinal photocoagulation scarring or melanoma can sometimes have similar appearances to the untrained.

- Visual loss occurs in retinitis pigmentosa (funnel visual field loss) and chorioretinitis (scotomas). Both funnel and tunnel vision refer to the phenomenon of peripheral visual field constriction, with preserved central vision (Fig. 5.67). *Funnel vision* results from disease of the peripheral retina. *Tunnel, or tubular, vision* is always non-organic or psychogenic. In tunnel vision, the visual field defect remains the same size (like looking through a tube) regardless of the distance of a target object. This is physically impossible, because a visual field subtends an arc, such that at double the distance an intact field should be doubled in size.

Feedback to patient

My junior colleague was very thorough and understandably concerned by the retinal appearances, but clearly this is a longstanding condition for you. We will of course focus on improving things from the point of view of the stroke and perhaps, when you are a little better, consider if there is anything further we might do with respect to helping you with your visual loss. We will of course make sure that the nursing staff and therapists take account of the visual problems you have when assessing and treating you.

Feedback to examiners

Summarise the key history and examination findings

This woman has webs of black pigment peripherally in both eyes. She appears to have some peripheral visual loss.

Provide a diagnosis or differential diagnosis with supporting evidence

She has retinitis pigmentosa. A differential diagnosis would be chorioretinitis due to *Toxoplasma* infection, cytomegalovirus infection or granulomatous diseases (e.g. sarcoidosis, tuberculosis). Some conditions associated with retinitis pigmentosa include Laurence–Moon–Biedl syndrome (mental retardation, hypogonadism, obesity, polydactyly, deafness and renal cysts), Kearns–Sayre syndrome (mitochondrial cytopathy with ophthalmoplegia, ptosis and heart block), Refsum's disease (a phytanic acid disorder comprising cerebellar ataxia, peripheral neuropathy and deafness), abetalipoproteinaemia (widespread neurological manifestations), Usher syndrome (sensorineural deafness), Friedreich's ataxia and mucopolysaccharidoses (Hurler's, Hunter's and Sanfilippo's syndromes).

Outline an investigation and management plan

Retinitis pigmentosa refers to a group of hereditary, progressive conditions that may be autosomal dominant, autosomal recessive or X-linked and that usually begin in childhood. Visual loss is unhappily not preventable.

CASE 5.26 CENTRAL RETINAL VEIN OCCLUSION

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Mr Robert Cooke, aged 77 years

This man has been admitted to the acute medical unit with sudden loss of vision.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 77-year-old man who has been referred to the acute medical unit with sudden, painless, partial loss of vision in your right eye. You have a history of primary open-angle glaucoma and ischaemic heart disease. You are understandably alarmed.

Focused history and examination

Initial history

- Ask about the visual loss. Patients with retinal vein occlusion typically present with sudden painless loss or distortion of vision, although occlusion of a branch retinal vein may be asymptomatic. If the sight-threatening complication of neovascular glaucoma develops, pain as well as loss of vision may also occur.
- Ask about past medical history.

Initial examination

- *Visual acuity* may be *unilaterally reduced*, depending on the extent of retinal involvement and if the macula is affected. Confrontational visual field testing may reveal *a peripheral visual field defect corresponding with an area of retinal non-perfusion in a branch retinal vein occlusion*. The affected side may have a *relative afferent pupillary defect* identified by constriction of both pupils when a bright light is shone into the normal eye, but initial dilation of both pupils when the light is then immediately shone into the affected eye because the stimulus passing through the affected optic nerve is weaker.
- Diagnosis is mainly based on typical abnormal findings on fundal examination. In central retinal vein occlusion there is a flock of *widespread retinal haemorrhages* in all quadrants of the retina (a 'blood-orange' appearance), which is an inevitable consequence of the pressure effects of occlusion. This may be accompanied by *dilated and tortuous retinal veins, cotton wool spots, macular oedema* (blurred appearance) and *optic disc oedema* (blurred swollen optic disc; Fig. 5.68). The overall appearance is like a fiery sunset (Fig. 5.69). In branch retinal vein occlusion only a sector of the retina is covered in haemorrhages though macular oedema may also be seen.
- Central retinal vein occlusion may be ischaemic or non-ischaemic (depending on whether the retina is ischaemic), and it is important to recognise signs of ischaemia because this has implications for prognosis. Box 5.36 lists the main signs of ischaemic central retinal vein occlusion. An ophthalmologist should perform fundus fluorescein angiography,

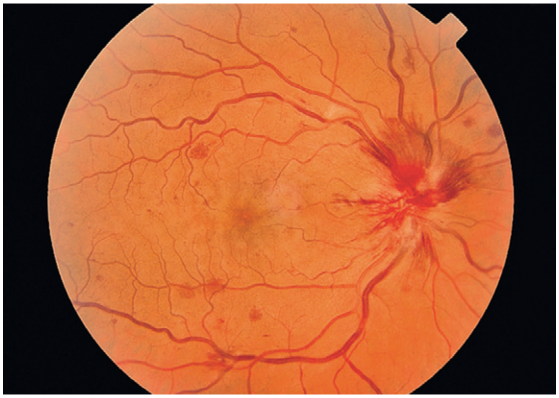


Figure 5.68 Optic disc swelling in central retinal vein occlusion (in this case caused by hypertension).

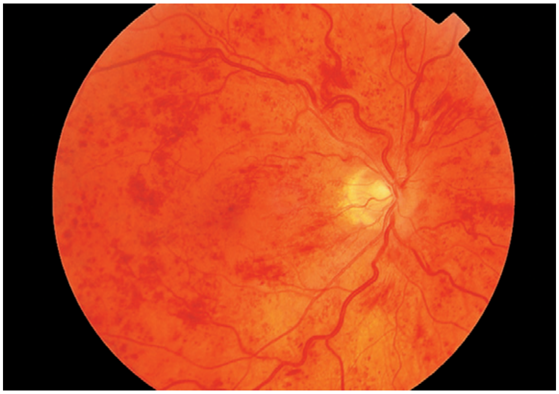


Figure 5.69 Central retinal vein occlusion.

Box 5.36 **Signs of ischaemic central retinal vein occlusion**

- Poor visual acuity (often < 6/60)
- Relative afferent pupillary defect
- Presence of multiple dark, deep intraretinal haemorrhages
- Presence of multiple (> 10) cotton wool spots
- Markedly dilated and tortuous retinal veins

which can distinguish between ischaemic and non-ischaemic retinopathy. If ischaemia has occurred, angiography typically shows extensive areas of capillary non-perfusion. Fluorescein angiography will also identify areas of capillary leakage. Leakage of dye indicates capillary leakage and therefore retinal oedema. Blockage of dye may be caused by capillary non-perfusion or retinal haemorrhage. The position of the haemorrhages can also help distinguish between these. Optical coherence tomography is used to measure the amount of oedema at the macula.

Further assessment

- Retinal vein occlusion – obstruction of the retinal venous system by thrombus formation, external compression, or disease of the vein wall – is the second most common retinal vascular disease after diabetic retinopathy. The prevalence is around 0.5–2.0% for branch retinal vein occlusion and 0.1–0.2% for central retinal vein occlusion. Compression of the retinal vein by a thickened adjacent retinal artery (typically by atherosclerosis or arteriosclerosis) is the most common cause of retinal vein occlusion. Retinal vein occlusion may occur in the central retinal vein, where the central retinal vein exits the eye or proximal to the lamina cribrosa of the optic nerve, or in a branch retinal vein at an arteriovenous crossing. Branch retinal vein occlusion may represent the end stage of arteriovenous nipping, in which the vein is compressed by the crossing artery without being completely occluded. If the superior or inferior branch of the central retinal vein becomes obstructed, a hemicentral retinal vein occlusion occurs and the corresponding half of the retina is affected. Retinal vein occlusion typically occurs in people aged over 50 years, with an equal sex distribution. Table 5.41 summarises the main risk factors. People over the age of 50 with high blood pressure, and those under 50 with hypercholesterolaemia, are particularly at risk.
- Conditions that can mimic retinal vein occlusion include papillophlebitis and diabetic papillitis, in both of which the swollen optic disc is the main feature, with localised retinal haemorrhages around the optic disc.
- Explore obvious concerns.

Feedback to patient

The symptoms you describe suggest a blockage to the retinal vein. This blockage has probably arisen as a result of a blood clot, which may have arisen because of the glaucoma or because of hardening of the blood vessels in the eye. I would like to arrange some blood tests and ask an ophthalmologist to see you urgently to see if there is anything that can be done now. I'm afraid I cannot tell you at this stage what the prospects are for recovery of vision in the eye, but we will do all we can to help you, and without delay. I'd be happy to answer any questions that I can.

Table 5.41 Risk factors for retinal vein occlusion

Risk factor	Comments
Hypertension	The main risk factor in those > 50 years, more common in branch retinal vein occlusion than in central retinal vein occlusion
Hyperlipidaemia	Cholesterol > 6.5 mmol/l is the main risk factor in those < 50 years, associated with retinal vein occlusion in about 50% of older patients
Diabetes	May reflect cardiovascular risk factors
Renal disease	Independent risk factor
Glaucoma	Association with central and branch retinal vein occlusion
Thrombophilia	Antiphospholipid syndrome, hyperhomocysteinaemia, factor V Leiden, protein C or S deficiency and antithrombin deficiency may be associated
Oral contraceptive	The most common association in young women
Optic disc vasculitis	To be considered especially where cardiovascular risk factors are absent
Multiple myeloma and myeloproliferative disorders	
Systemic inflammatory diseases	Including small-vessel vasculitis, polyarteritis nodosa, Goodpasture's syndrome, sarcoidosis, Behçet's syndrome

Feedback to examiners

Summarise the key history and examination findings

This man has a flock of haemorrhages throughout the retina, retinal vein dilatation, and optic disc swelling.

Provide a diagnosis or differential diagnosis with supporting evidence

He has a central retinal vein occlusion.

Outline an investigation and management plan

The cause is likely to be arteriosclerosis or glaucoma, but hyperviscosity states should also be considered and investigated for. He needs immediate assessment by an ophthalmologist [Box 5.37].

Box 5.37 **Investigation and management of retinal vein occlusion**

Optimal management of retinal vein occlusion has medical and ophthalmological components.

Medical management

Investigations in all patients include full blood count and erythrocyte sedimentation rate or plasma viscosity, urea, electrolytes, creatinine, blood glucose and lipids, thyroid function, myeloma screen and electrocardiography. Other tests might include C-reactive protein, a thrombophilia screen and autoantibodies.

Medical management is aimed at the identification and treatment of modifiable risk factors (commonly blood pressure, lipids and diabetes), aiming to prevent further non-ocular target organ damage and recurrence of venous occlusion, particularly in the fellow eye. Aspirin is indicated in patients with hypertension if the 10-year risk of coronary heart disease is > 15% or the 10-year risk of total cardiovascular disease is > 20%, providing blood pressure control is satisfactory and there is no contraindication. Patients taking antiplatelet agents or anticoagulants when they develop a central retinal vein occlusion tend to have more severe haemorrhages and a worse visual outcome and the Royal College of Ophthalmologists does not recommend aspirin otherwise. Oestrogen-containing hormone replacement therapy is relatively contraindicated in women with retinal vein occlusion. However, continued use does not seem to be associated with a higher rate of recurrence. The oral contraceptive pill is the most common underlying association in young women, and should be prescribed with caution in retinal vein occlusion. Rarer underlying conditions such as myeloma and inflammatory disorders should be managed by appropriate specialists.

Ophthalmological management

Ophthalmological treatments focus on the prevention and management of the main sight-threatening complications – ocular neovascularisation and macular oedema. Patients with haemorrhagic retinopathy need early management by an ophthalmologist for better visual outcomes.

Management of ocular neovascularisation

Patients with ischaemic central retinal vein occlusion can develop neovascularisation, which may lead to painful neovascular glaucoma that can be difficult to treat. New vessels can develop on the retina, on the iris and in the angle between the cornea and the iris through which aqueous fluid normally leaves the eye. In non-ischaemic central retinal vein occlusion neovascular glaucoma is rare.

Laser panretinal photocoagulation is beneficial in central retinal vein occlusion when new iris or angle vessels are visible. Peripheral scatter laser photocoagulation of ischaemic retina is beneficial with retinal and disc neovascularisation. The precise mechanism of action of photocoagulation is unknown and it may reduce the hypoxic state of the retina by destroying oxygen-consuming photoreceptor cells, but potential adverse effects include reductions in visual acuity, visual field, colour vision, night vision and contrast sensitivity; pain, choroidal neovascularisation, haemorrhage, epiretinal fibrosis, and serous detachment of the peripheral retina are possible. More recent evidence indicates that intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents in combination with panretinal photocoagulation results in dramatic regression of neovascularisation. These treatments can be repeated if new vessels recur.

If neovascular glaucoma is established and the eye is blind, the aim is to keep the eye pain free, usually with topical steroids and atropine. But if the eye has visual potential, it is important to try to control intraocular pressure with topical pressure-lowering agents or surgery to preserve vision. Intracameral (into the anterior chamber) and intravitreal bevacizumab (an anti-VEGF agent) cause regression of new iris vessels and reduce obstruction of the angle.

Management of macular oedema

Macular oedema, thought to be caused by leakage of fluid from capillaries in the central macular area, is the most common cause of visual loss in patients with retinal vein occlusion.

Laser photocoagulation has traditionally been used to treat macular oedema secondary to branch retinal vein occlusion. Grid laser photocoagulation in the area of leaking capillaries (recommended 3–6 months after the event and absorption of most of the haemorrhage) is, however, of no benefit on visual acuity in central retinal vein occlusion. Patients with severe visual loss (< 6/60 vision) and those who have had symptoms for more than a year are also unlikely to benefit from laser treatment.

Corticosteroids reduce retinal capillary permeability and inhibit the expression and metabolic pathway of VEGF, a driver of macular oedema. Trivaris, a preservative-free form of intravitreal triamcinolone, may help over 25% of patients with central retinal vein occlusion but does not appear superior to laser treatment in branch retinal vein occlusion. Dexamethasone is more potent and dexamethasone implants appear beneficial, safe and cost effective in retinal vein occlusion and are approved by the National Institute for Health and Clinical Excellence.

Blocking VEGF appears beneficial. Ranibizumab blocks all isoforms of VEGF and is given by injection and may become more widely licensed. VEGF Trap-Eye is a fusion molecule with anti-VEGF effects. Bevacizumab is a pan-VEGF blocker unlicensed for intraocular use. Intravitreal pegaptanib is also being studied. Anti-VEGF drugs increase the risk of stroke and cardiovascular events when used to treat age-related macular degeneration; this may also be true for retinal vein occlusion.
Combinations of laser, corticosteroid and anti-VEGF treatments may have a place.

Prognosis if untreated or treated conservatively

Not all retinal vein occlusions need treatment. Subsequent visual acuity seems to depend on visual acuity at presentation and eyes with an initial visual acuity of at least 6/12 are more likely to retain good vision, and patients with central retinal vein occlusion under 45 years are likely to have a better outcome. The incidence of new vessels on the iris or neovascular glaucoma in untreated or conservatively managed participants with central retinal vein occlusion is 4.2%, and that of retinal neovascularisation (including vitreous haemorrhage) is 7.5%. Ischaemia with subsequent neovascularisation is not uncommon in branch retinal vein occlusion, but neovascular glaucoma is rare. Branch retinal vein occlusion in the other eye occurs in about 10% of cases over time.

CASE 5.27 CENTRAL RETINAL ARTERY OCCLUSION

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Mr Harold Sargent, aged 82 years
>
> This man has been admitted with sudden loss of vision.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are an 82-year-old man who has been referred to the acute medical unit with sudden, painless loss of vision in your left eye. You have atrial fibrillation. You take digoxin, but not warfarin. You are otherwise well. You are alarmed to have lost your vision.

Focused history and examination

Initial history

- Ask about the visual loss – partial or complete, sudden or gradual, other symptoms; there is usually a history of sudden painless visual loss.

Initial examination

- Perform fundoscopy.

The *retina is pale*. In the first few days a *cherry red spot* is present at the fovea because the red choroid is visible at the fovea where the retina is rendered especially thin (Figs 5.70 and 5.71). The entire fundus is otherwise *oedematous* with a *milky appearance*. The *arterioles* are *thin*. Neovascularisation ultimately occurs but is never overt, probably because retinal destruction limits the amount of angiogenic factor the retina can produce.

The central retinal artery divides into upper and lower branches on the disc to supply a ‘half moon’ of retina above and below the horizontal meridian respectively. Branch occlusion as opposed to central occlusion therefore only causes visual field defects in areas corresponding to the retinal supply of the branch and these are limited by the horizontal meridian.

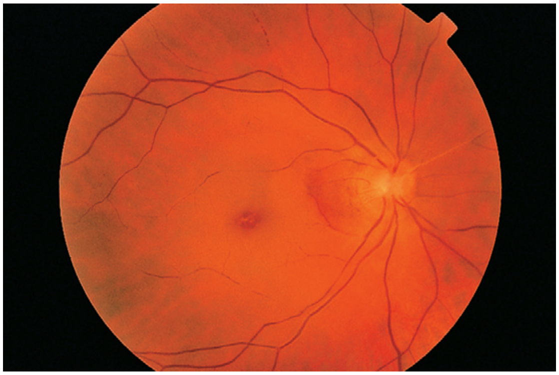


Figure 5.70 Central retinal artery occlusion. Note the cherry red spot at the macula, the creamy pallor of the fundus and the wispy appearance of the vessels.

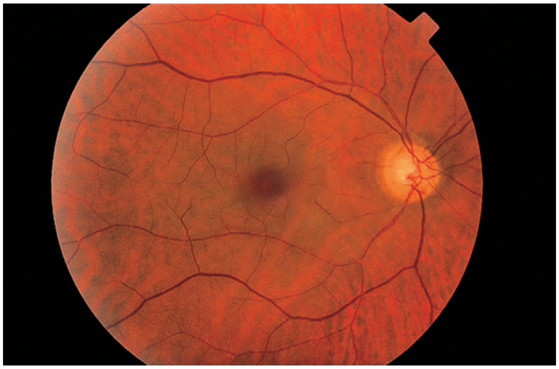


Figure 5.71 Central retinal artery occlusion. Note how a deeply pigmented retina (which is normal) can alter the colour and appearance of retinal signs.

Further assessment

- Consider embolic sources. Retinal artery occlusion often results from atrial fibrillation (known or unknown), mural thrombus (following myocardial infarction) or giant cell arteritis (more commonly the result of anterior ischaemic optic neuropathy damaging the optic nerve head). Occasionally a cholesterol embolus may be visible in a vessel. Cholesterol emboli may occur as a complication of procedures disrupting the endothelium (such as percutaneous coronary intervention). The dislodged emboli may cause visual disturbances, strokes, renal failure or peripheral vascular occlusion.
- Explore obvious concerns.

Feedback to patient

> The symptoms you describe suggest a blockage to the retinal vein. This blockage has probably arisen as a result of a blood clot, which may have arisen because of the glaucoma or because of hardening of the blood vessels in the eye. I would like to arrange some blood

tests and ask an ophthalmologist to see you urgently to see whether there is anything that can be done now. I'm afraid I cannot tell you at this stage what the prospects are for recovery of vision in the eye, but we will do all we can to help you, and without delay. I'd be happy to answer any questions that I can.

Feedback to examiners

Summarise the key history and examination findings

This man has a pale retina and thin vessels.

Provide a diagnosis or differential diagnosis with supporting evidence

I think this may be central retinal artery occlusion.

Outline an investigation and management plan

The cause is likely to be atrial fibrillation. Retinal artery occlusion is the stroke to the transient ischaemic attack that is amaurosis fugax. Investigations are directed at determining an embolic source (carotid imaging, electrocardiogram, echocardiography); neuroimaging is usually not necessary. Treatment is with antiplatelet therapy, consideration of carotid endarterectomy and management of any cardioembolic source with anticoagulation. Secondary prophylaxis of hypertension and hypercholesterolaemia are important, the latter sometimes responsible for cholesterol emboli. Admission to an acute stroke unit, however, is not necessary as other aspects of stroke care such as prevention of aspiration and early rehabilitation are not relevant and urgent outpatient investigations are often appropriate. He also needs the immediate opinion of an ophthalmologist.

CASE 5.28 RETINAL DETACHMENT AND VITREOUS HAEMORRHAGE

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mrs Heather Forbes, aged 70 years

This woman is in your medical outpatient clinic and reports the symptom of flashing lights in the corner of her eye earlier today that lasted for about 10 minutes.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old woman in the medical outpatient clinic and mention to the doctor that earlier on today you experienced flashing lights in the corner of your eye. The phenomenon lasted for about 10 minutes. Vision does not seem to have been affected. You are short-sighted. You are concerned because a friend lost her vision as a result of blood pressure and diabetes.

Focused history and examination

Initial history

- Explore the history of any floaters or flashing lights (Box 5.38), and ask about any visual loss.

Initial examination

- Perform fundoscopy. This will probably be normal if symptoms have been brief and without visual loss.

Further assessment

- Check visual acuity and visual fields for any area of visual field loss or scotoma on an axis corresponding to an area of detached retina. Visual loss will help to differentiate uncomplicated posterior vitreous detachment (PVD) from retinal detachment.

Box 5.38 Floaters and flashing lights

Floaters (the perception of mobile spots, lines or haze)

These are usually the result of opacities in the vitreous. They may be caused by:

- Vitreous syneresis (degeneration) and age-related macular degeneration
- Posterior vitreous detachment, which often makes opacities more mobile and hence more noticeable
- Vitreous haemorrhage
- Inflammatory infiltrates, e.g. in posterior uveitis.

Flashing lights (photopsia or perception of light not attributable to an incident light)

The origin of light flashes is less well understood, but they probably result from retinal stimulation by vitreoretinal traction. Flashes are a classic feature of posterior vitreous detachment (often recurrent, brief events in the peripheral temporal field but may occur anywhere) and incipient retinal detachment, but they may also occur in migraine with aura, and occasionally with choroidal tumours or postural hypotension.

- Understand the pathophysiology of PVD, retinal detachment and vitreous haemorrhage, explained below.
- Then note any high-risk features in patients experiencing floaters or flashing lights (Box 5.39), and common risk factors for retinal detachment – age, myopia, previous trauma (see Table 5.42).
- Explore any concerns.

Posterior vitreous detachment (PVD)

Explore the symptoms further. PVD may occur acutely, causing *flashes* (vitreoretinal traction) and *floaters* (glial tissue which normally attaches the vitreous to the retina is exposed, and an associated tear in the retina may produce a shower of floaters if specks of blood or other bits of degenerate matter spurt into the vitreous from torn vessels and tissue) or may be of gradual onset with intermittent floaters. Any visual field defect, or blurring or distortion of vision, could also represent PVD.

Box 5.39 **High-risk features in patients experiencing floaters or light flashes**

- Acute onset suggests posterior vitreous detachment, a retinal tear or retinal detachment
- Visual blurring
- Reduced visual acuity (suggests macular detachment or vitreal haemorrhage) or visual field defect
- Previous history or family history of retinal tear or detachment
- Myopia
- Previous ocular trauma or surgery
- Diabetes

PVD is usually highly suspected from a history of abrupt and overt flashes that appear like an electrical storm or fireworks in a segment of one eye's visual field, with or without a shower of floaters. Isolated, brief sparks, rather than full-blown firework displays, especially at night (e.g. getting up to the bathroom) are usually not significant, nor are one or two floaters, which usually represent degenerate clumps of cells entering the vitreous. Longstanding intermittent floaters are usually benign and caused by vitreous degeneration, and patients with these warrant review if their floaters change or their vision becomes affected.

Patients with floaters or light flashes warranting assessment by an ophthalmologist are those with high-risk features (Box 5.39).

Retinal detachment

Retinal detachment refers to separation of the neuroretinal cell layer and its underlying pigment layer, and not separation of the retina from the underlying choroid. PVD,

Table 5.42 Risk factors for retinal detachment

	Risk factor / cause	Comment
Rhegmatogenous Caused by breaks in the retina	Age	An intact vitreous of normal viscosity is important in keeping the retina in place; with advancing age viscosity decreases, and the 'fluid vitreous' is capable of creeping behind any small neuroretinal tear that might result from vitreous collapse and posterior vitreous detachment
	Myopia	The eye is 'too big' for its retina, which is 'stretched and thinned' and susceptible to tearing; myopic people are more likely to develop retinal detachment at a younger age
	Trauma	May cause direct retinal detachment or produce scarring which can exert abnormal tractional forces on the retina
	Cataract surgery	Can alter vitreous volume or shape
	Marfan's syndrome	Weakness in connective tissue
Tractional Caused by chronic traction from scars on the retinal surface and across the vitreal cavity	Neovascularisation (proliferative diabetic retinopathy or vitreopathy) Sickle cell retinopathy Central retinal vein occlusion	New blood vessel formation in diabetes may change adhesive forces between the vitreous and retina; vasculitis can cause similar problems
Exudative Caused by leakage of fluid into the subretinal space	Inflammatory	e.g. uveitis, sarcoidosis
	Hydrostatic	e.g. malignant hypertension, pregnancy, toxaemia
	Congenital retinal abnormalities	May sometimes not become manifest until later life
	Ocular tumours	Rarely, pressure from behind the retina such as that caused by a choroidal tumour causes retinal detachment
	Maculopathy	Neovascular

in which the posterior vitreous separates from the retina, is the main event predisposing to retinal detachment.

PVD may simply exert traction on the retina and then release it without tearing it. Indeed, PVD without subsequent retinal detachment is very common.

But as the vitreous collapses, traction on the retina (with which it is normally in tight adherence) may cause a retinal tear, which in turn can lead to separation of the neuroretinal and pigment retinal layers and detachment of the neuroretina. If PVD results in retinal detachment or haemorrhage, visual impairment is very likely, and if the macula is torn or obscured, central vision is abruptly lost. The classic symptom of retinal detachment is that of a curtain being drawn across the visual field. Detachment may be visible at ophthalmoscopy, although the narrow field of view does not exclude detachment. The *retina appears opaque* and its reflex is *grey* rather than pink (the normally transparent retina becomes opaque in any profile other than its normal attached position and obscures the underlying red choroid) (Fig. 5.72). *Rippling* may be visible if the detached retina folds into hills and valleys because of any subretinal fluid.

Risk factors for retinal detachment are listed in Table 5.42. Whilst most are *rhegmatogenous*, implying a tear, and of these most are due to PVD as a result of an ageing, shrinking vitreous, less common groups of causes include *tractional* and *exudative*.

Vitreous haemorrhage

Vitreous haemorrhage (Box 5.40) causes floaters and reduced vision. Large bleeds cause loss of the red reflex (other causes of this include cataracts and, rarely, asteroid hyaline bodies and retinoblastomas).

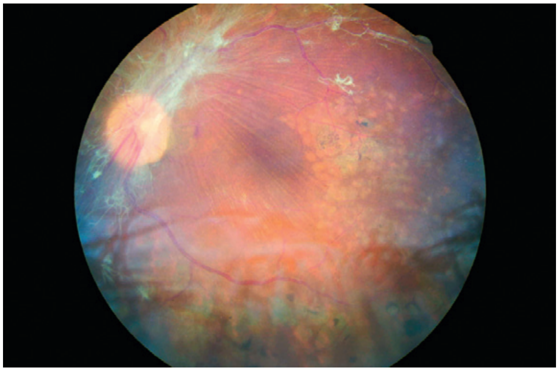


Figure 5.72 Retinal detachment/traction.

Box 5.40 Causes of vitreous haemorrhage

- Posterior vitreous detachment
- Proliferative diabetic retinopathy
- Retinal vein occlusion
- Subarachnoid haemorrhage (often limited to subhyaloid rather than vitreous haemorrhage)
- Trauma
- Vasculitis

Feedback to patient

> Flashing lights suggest that a small piece of the jelly inside the eye has pulled away from and tugged on the retina. It is a common symptom, often more likely in people who are short-sighted, and the symptom does not in itself suggest a full-blown retinal detachment. It is reassuring that vision seems to be unaffected. However, it would be sensible for us to send you along to the same-day eye clinic for a thorough check on the retina by an ophthalmologist. I can reassure you that there are absolutely no changes in the eye suggesting eye problems from blood pressure or diabetes. Let me know if that all makes sense, and I'd be happy to answer any other questions that I can.

Feedback to examiners

Summarise the key history and examination findings

> This woman has experienced isolated flashing lights for a brief period in one eye.

Provide a diagnosis or differential diagnosis with supporting evidence

> The absence of substantial floaters or loss of vision suggests posterior vitreous traction or detachment without retinal tearing or detachment.

Outline an investigation and management plan

> She should see an ophthalmologist urgently to confirm that there has not been a retinal tear. Laser photocoagulation or cryotherapy may be used to repair a tear and is very successful although evidence for prophylactic treatment of asymptomatic tears preventing retinal detachment is lacking. Once detached, common treatment options include scleral buckling and primary vitrectomy with gas tamponade. New tissue adhesives are being developed. Treatment of a detached retina is seldom possible if the neuroretinal layer has become ischaemic and fibrosed.

CASE 5.29 AGE-RELATED MACULAR DEGENERATION AND OTHER RETINAL PROBLEMS – DRUSEN, ANGIOID STREAKS AND MYELINATED NERVE FIBRES

Candidate information

Role

You are a doctor on the stroke unit.

Scenario

> Re: Mr John Braithwaite, aged 65 years
>
> This man is in hospital with a stroke and your junior doctor colleague has asked you to examine his fundi, which he believes to be abnormal.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 65-year-old man in hospital following a stroke. You are progressing well. A diligent junior doctor examined your eyes because you mentioned that your vision has been a little less good over the past 2 years, and has asked his senior to do so as well.

Focused history and examination

Initial history

- Ask about the visual loss – partial or complete, sudden or gradual, other symptoms; there is usually a history of gradual central painless visual loss.

Initial examination

- Perform fundoscopy.

Drusen in the area of the macula, individually or in clusters (Fig. 5.73), mask the normally transparent retina and its underlying red choroid. There may also be frank *macular atrophy* exposing the white sclera beneath. There may even be areas of *haemorrhage* that mask all underlying structures. The disrupted pigment retinal layer may exhibit areas of *hypopigmentation* or *hyperpigmentation*. The overall appearance of these various changes can be like a *splodge of mixed paints* spilt over the macula (Fig. 5.74). The overall consequence is loss of *central vision*.

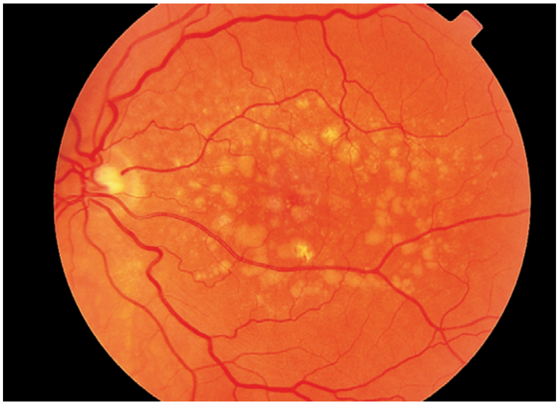


Figure 5.73 Typical drusen (heralding age-related macular degeneration).

Further assessment

- Ask about visual distortion. This is a specific and sensitive symptom of choroidal neovascularisation seen in 'wet' age-related macular degeneration (AMD).
- Explore any concerns.

AMD is the commonest cause of central vision disturbance and registered blindness in the UK. Causes include genetic predisposition, age and smoking. Because cataracts and AMD are common in older people, it may be difficult to diagnose AMD with fundoscopy as even early cataracts may obscure adequate fundoscopy; but typically patients with cataracts find that reading is easier when a light is shone directly onto the page and visual enhancement with such a simple measure suggests that AMD is not present (of course it cannot exclude AMD). Visual loss in AMD may occur from neovascular abnormalities and haemorrhage ('wet' AMD) (Fig. 5.75) or non-neovascular abnormalities ('dry' AMD) (Box 5.41).

Occasionally angioid streaks or myelinated nerve fibres may be mistaken for AMD.

Angioid streaks

These are *dark red trails* or *streaks with irregular edges* (Fig. 5.76). They represent cracks in the retina and Bruch's membrane through which the choroid is exposed. They are uncommon. Many patients with angioid streaks have *pseudoxanthoma elasticum*, and they can also be a feature of Ehlers–Danlos syndrome, Paget's disease or sickle cell

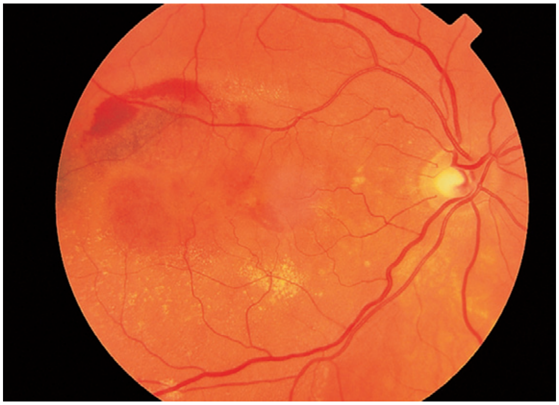


Figure 5.74 More advanced age-related macular degeneration with choroidal neovascularisation and haemorrhage. This patient would have marked impairment of central vision. Note that with choroidal haemorrhage the overlying retinal vessels can be clearly seen (compare with preretinal haemorrhage in diabetic retinopathy).

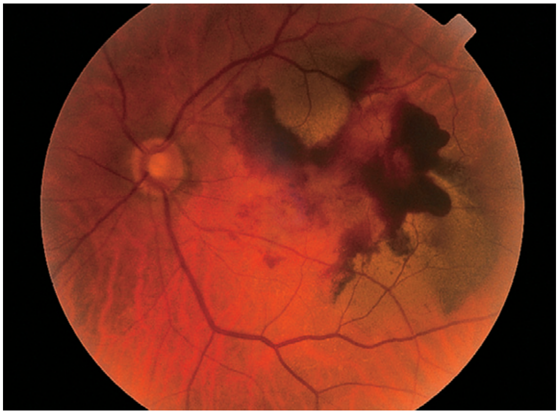


Figure 5.75 Extensive choroidal haemorrhage.

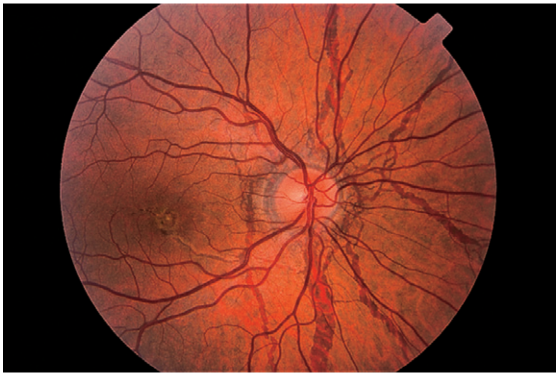


Figure 5.76 Angioid streaks.

Box 5.41 **Development of drusen and age-related macular degeneration (AMD) (asteroids)**

Drusen

Drusen are early features of AMD and appear as small, pale yellow deposits on the retina. They lie between the basement membrane of retinal pigmented epithelium and Bruch's membrane. Their pathogenesis remains uncertain, but they are probably derived from the debris of 'retired' retinal cells. They are commonly detected in people over the age of 65 without other signs of disease.

Wet AMD

In wet AMD (neovascular, exudative or disciform), vessels from the choroid layer (which normally nourish the pigment retina) proliferate across Bruch's membrane and into the subretinal space. Visual distortion (e.g. of printed words or grids) is a specific and sensitive symptom of choroidal neovacularisation. Visual loss occurs as these vessels haemorrhage or leak transudate into the subretinal space, the retina slowly becoming atrophic and fibrosed. Large haemorrhages may even cause retinal detachment. Choroidal neovascularisation itself may not be seen on direct ophthalmoscopy, requiring fluorescein angiography for detection.

Dry AMD (geographic atrophy or non-exudative AMD)

In dry AMD, the retina in the areas of drusen slowly atrophies, and visual deterioration is more gradual, often over many years. Visual distortion is not a feature. Macular dystrophy is sometimes mistaken for macular degeneration and is a rare genetic variant.

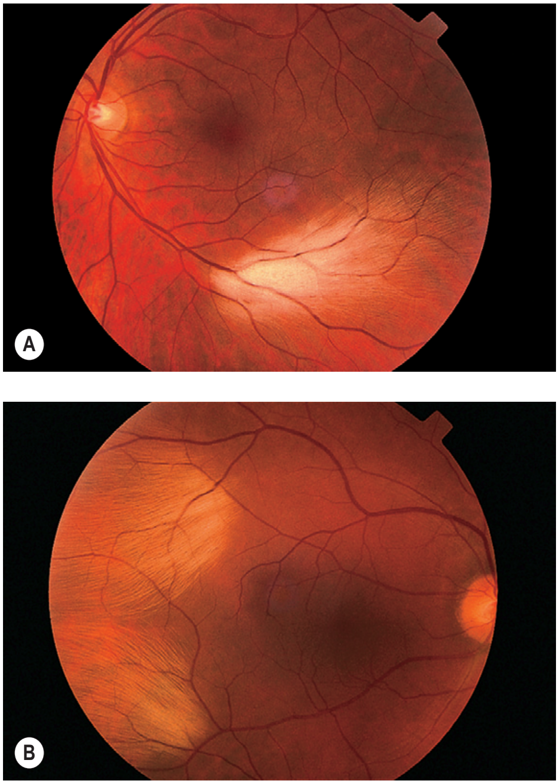


Figure 5.77 (A, B) Myelinated nerve fibres.

disease. Appearances are characteristic. Visual loss does not occur. The examiners are unlikely to know more about angioid streaks!

Myelinated nerve fibres

These are *bright white patches with frayed edges* (Fig. 5.77). They can look like an exploding white firework emanating from the optic disc or a bright comet trailing across the retinal sky! Myelination of optic nerve fibres is normally arrested before such fibres enter the eye. Failure of arrest during development results in myelinated (or medullated) nerve fibres. Appearances are characteristic. There may be visual field defects but frequently myelinated nerve fibres are asymptomatic.

Feedback to patient

My junior doctor was concerned about the possibility of a condition called age-related macular degeneration, which can show up as a series of small deposits at the back of the eye. Briefly it means that some of the retinal cells are less effective than they once were and a little more prone to breakdown. On examining your eye I think you may have very early signs of where pockets of cells have degenerated. I don't think any action is needed at all immediately but routine referral to an eye specialist would be appropriate. I'd be happy to try to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has significant areas of drusen formation, possibly with some atrophic patches. There does not appear to be any neovascularisation and he reports mild loss of central vision without visual distortion.

Provide a diagnosis or differential diagnosis with supporting evidence

He has drusen and possibly dry age-related macular degeneration.

Outline an investigation and management plan

He probably requires only surveillance by the eye clinic.

Laser photocoagulation therapy can deliver thermal energy under topical anaesthesia to areas of neovascularisation, but because this treatment also destroys the retina it often cannot be delivered to the areas of greatest need (most patients needing treatment have choroidal neovascularisation extending under the central retina). The closer the treatment to eloquent areas of retina, the higher is its risk–benefit ratio. In an attempt to solve this dilemma, photodynamic therapy emerged as a favoured alternative. The principle of this therapy is that a drug that can be photoactivated to destroy tissue locally is given intravenously. When it circulates into the new choroidal vessels, photoactivation is applied. Treatments inhibiting vascular endothelial growth factor (e.g. pegaptanib, ranibizumab, bevacizumab), some administered intravitreally, are now proving optimal, perhaps combined with photodynamic therapy; pegaptanib specifically blocks vascular endothelial growth factor 165, the major angiogenic form of vascular endothelial growth factor.

In addition to regular outpatient follow-up, patients with drusen may be taught to screen themselves frequently using such techniques as looking at the fine lines on a piece of graph paper for any black spots or areas of distortion which may indicate underlying neovascularisation.

CASE 5.30 RED EYE AND OTHER ANTERIOR EYE PROBLEMS – UVEITIS, CATARACTS, GLAUCOMA

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Andrew Ellis, aged 70 years

This man is in hospital and appears to have developed a red eye.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old man in hospital with an exacerbation of inflammatory bowel disease. You have developed a painful, red eye. You have a background history of mild cataracts and chronic glaucoma and are very concerned that you seem to have so many problems with your eyes.

Focused history and examination

Initial history

- Ask about the redness and pain – onset, painful or painless.
- Ask about the visual loss – partial or complete, sudden or gradual, other symptoms. Visual loss is variable with cataract and glaucoma.
- Ask about past medical history.

Initial examination

- Look at the eye and attempt fundoscopy (this may be thwarted by cataracts).

Red eye

Either there is evidence of previous eye disease with scarring (Fig. 5.78) or the eye is *red, predominantly close to the corneoscleral limbus*. Ask about pain. Simple conjunctivitis causes predominantly peripheral, conjunctival redness and does not extend to the limbus and tends to be irritating rather than painful.

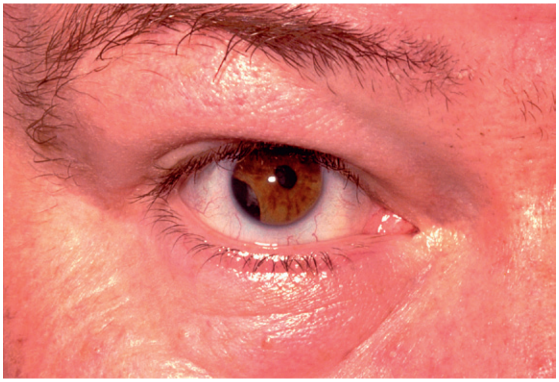


Figure 5.78 Old iritis.

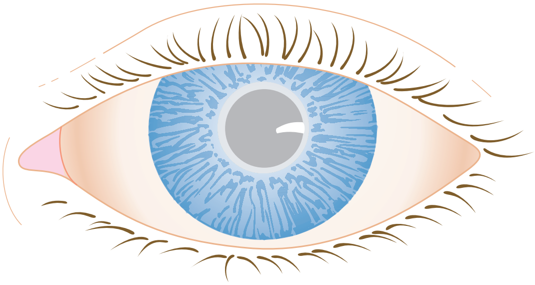


Figure 5.79 Cataract.

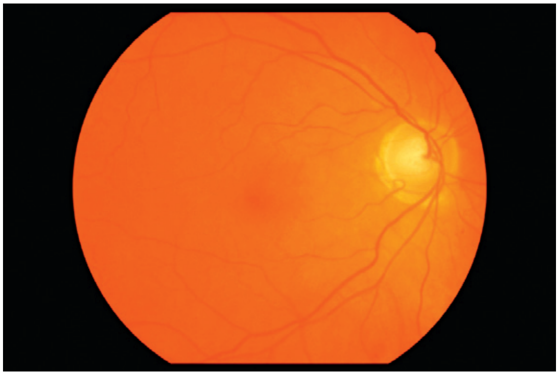


Figure 5.80 Glaucoma with cupping.

Cataract

There is *loss of the red reflex* and the lens appears cloudy (Fig. 5.79).

Glaucoma

There is *cupping* of the *optic disc* (Fig. 5.80). Primary open-angle glaucoma is insidious, often being without symptoms until considerable ocular damage has been sustained. Patients may present because of visual field loss but are frequently referred from optometrists following the detection of raised intraocular pressure.

Further assessment

- Be aware of the causes of red eye, and a little about cataracts and primary open-angle glaucoma. These are explained below.
- Explore concerns.

Red eye

A distinguishing feature between most of the serious, sight-threatening causes of red eye from non-threatening conjunctivitis is that in the former the redness dominates at the corneoscleral limbus (where blood vessels emerge from the depths of the eye). This is sometimes called ciliary injection. Furthermore, serious causes are usually painful. The causes of a painful, red eye that are medical emergencies are uveitis (iritis), acute closed-angle glaucoma and keratitis (Box 5.42).

Cataracts

These may be subtle but symptoms and ophthalmoscopy are usually sufficient for more overt cataracts. Most cataracts arise because of ageing of the crystalline lens. The lens continues to grow through life and new fibres are laid down and old ones not replaced. Yellowing of the nucleus is common with ageing (nuclear sclerosis). The transparency of the lens is a result of many factors, including its chemical consistency. Extrinsic causes of cataract are listed in Box 5.43.

Symptoms of different types of cataract are described in Box 5.44.

Chronic primary open-angle glaucoma

In primary open-angle glaucoma there is resistance to outflow through the meshwork owing to partial obstruction and additional poorly understood mechanisms. There are three cardinal features of primary open-angle glaucoma (Box 5.45). Risk factors include the level of intraocular pressure, age, genetics and family history, Afro-Caribbean origin, a thin cornea, a large cup to disc ratio and myopia.

Normal intraocular pressure is 10–21 mmHg. Raised intraocular pressure with normal visual fields and discs is called ocular hypertension. The mechanisms behind the triad of features in primary open-angle glaucoma can be explained as follows.

1. The pathophysiological changes in primary open-angle glaucoma have traditionally been attributed to raised intraocular pressure causing damage to the optic nerve head (optic disc). Increasingly, vascular and toxic damage to optic nerve fibres are thought to contribute, and 'primary open-angle glaucoma' with normal intraocular pressure is recognised. Ageing has a role, and the optic nerve, which at birth contains approximately 10^6 neurons, loses about 10^4 of these per year.
2. A normal optic disc contains a central cup, an indentation or cavity from which the blood vessels emanate. It is normally shallow and the ratio of the

Box 5.42 **Causes of a painful red eye**

Uveitis / iritis

The uveal tract comprises the anterior uvea (iris and ciliary body) and the posterior uveal tract (choroids – the vascular layer which supplies the outer pigment retina). Uveitis may affect the anterior or posterior uvea or both (panuveitis). Uveitis typically produces a painful, watery, photophobic red eye with blurred vision due to the presence of inflammatory cells. The pupil is small and in spasm in iritis and adhesions between the iris and anterior lens capsule (posterior synechiae) may render it irregularly shaped. There may be keratitic precipitates (clumps of white cells on the inner lining of the cornea and floating in the anterior chamber appear like dust in a beam of light) and precipitation of neutrophils in the anterior chamber may result in a hypopyon. Anterior uveitis is classically associated with human leucocyte antigen (HLA) B27 conditions such as ankylosing spondylitis (up to 20% of patients), Reiter's syndrome and psoriatic disease. It occurs in most patients with Behçet's disease (a multisystem vasculitis also causing oral and genital ulceration). Inflammatory bowel disease, sarcoidosis and tuberculosis can cause anterior or posterior uveitis (chorioretinitis), as can a wide range of other infections including toxoplasmosis, toxocariasis, human immunodeficiency virus and the herpes simplex and zoster viruses.

Acute (closed-angle) glaucoma

Normally the ciliary body secretes aqueous, which flows into the posterior chamber between the lens behind and the iris in front, and then through the pupil into the anterior chamber. It leaves the eye through the trabecular meshwork, flowing into Schlemm's canal and into episcleral veins. In acute glaucoma, there is complete obstruction to outflow caused by sudden closure of the drainage angle; apposition of the lens to the back of the iris prevents flow of aqueous from the posterior chamber to the anterior chamber. This is more likely when the pupil is semi-dilated at night (iris shortened and fattened). Aqueous then collects behind the iris and pushes it forwards onto the trabecular meshwork and acute block to drainage occurs, leading to rapidly rising intraocular pressure. Acute glaucoma usually arises in long-sighted (hypermetropic) people, who tend to have shallow anterior chambers or short eyeballs. It may also occur in rubiosis of the iris and in anterior uveitis (inflammation of the eye) when adhesions may develop between the lens and iris (posterior synechiae). It may be precipitated by dilating drops and mydriatics such as tricyclics. It is very painful. The cornea is steamy / cloudy / stormy with a mid-dilated unreactive pupil, and the anterior chamber is narrow. It is an emergency.

Keratitis

The cornea may be damaged by trauma (corneal abrasions or penetrating eye injury), foreign bodies and infection. Keratitis and ulceration caused by herpes simplex or zoster infections may assume a punctate or dendritic pattern. Keratitis usually presents with pain, redness and lacrimation. Bacterial ulceration may result in a hypopyon. Keratitis may also arise as a sterile immunological response to antigens. An example is marginal keratitis where staphylococcal exotoxin triggers marginal inflammation of the cornea with ciliary injection. It is often the result of staphylococcal overgrowth in patients with blepharitis. When assessing a corneal problem, the eye should be examined completely with appropriate stains, and a safe rule is that topical steroids should never be commenced without ophthalmological recommendation. A rare 'corneal melt' condition is an immunological keratitis associated with autoimmune conditions such as Wegener's granulomatosis.

Scleritis and episcleritis

Scleritis may be a feature of vasculitis, sarcoid, rheumatoid disease, systemic lupus erythematosus, inflammatory bowel disease and ankylosing spondylitis. Patients with rheumatoid disease may also develop scleromalacia perforans, a necrotising scleritis which gives the eye a grey-blue tinge. The grey-blue tinge results from thinning of the sclera, faintly exposing the choroid pigment beneath. Osteogenesis imperfecta, Ehlers–Danlos syndrome and Marfan's syndrome may also cause blue sclera.

Episcleritis produces superficial redness, usually without significant pain. It may be associated with rheumatoid disease but is usually an idiopathic self-limiting condition.

Box 5.43 **Causes of cataract**

- Smoking
- Diabetes (most commonly early-onset age-related type but occasionally 'snowflake' cortical opacities)
- Corticosteroids
- Wilson's disease (stellate cataracts)
- Hypoparathyroidism
- Congenital (familial, myotonic dystrophy, infection)
- Trauma (including radiation)
- Malnutrition
- Acute dehydration
- Cumulative sunlight exposure

cup diameter to the disc diameter is normally around 1 : 3. Discs are like shoe sizes, however, varying between individuals and, when examining cup–disc ratios, asymmetry between the eyes and progression over time are more important than a 'snap-shot' appearance. As primary open-angle glaucoma progresses, neurons are lost and the cup becomes a deepening and expanding cave into which the blood vessels appear to dive.

3. The classic field defect in primary open-angle glaucoma is an arcuate scotoma of peripheral visual loss, with relative preservation of macular or central vision (Fig. 5.81); visual acuity may be 6 / 6. There are two considerations when explaining the field defect. The first is that the ratio of visual receptors (R) to their attached neurons (N) running to the disc is much greater at the periphery (R : N, around 8 : 1) than at the macula (R : N, 1 : 1). For every neuron lost from peripheral vision, multiple receptors are lost. Secondly, the organisation of nerve fibres is such that those from the macula run directly to the disc while those from the periphery must 'arc' around the macula, tending to reach the disc at its vertical north and south poles. These poles tend to be damaged first in primary open-angle glaucoma, resulting in an

Box 5.44 Symptoms of different types of cataract

Nuclear cataracts

These produce gradually reduced contrast and colour intensity and ultimately difficulty seeing faces, number plates and so forth. It is like looking through a rippled window. Reading is often surprisingly good.

Cortical cataracts

These scatter light from localised opacities and disrupt its smooth transmission. This produces a whitewash behind the window or dirty window sensation, glare when driving, especially from car headlights at night, and difficulty reading. Sunlight is uncomfortable on a winter's day when low in the sky.

Subcapsular cataracts

Opacification of the posterior cortical zone occurs in a posterior subcapsular cataract. These are visually disabling in good lighting but less troublesome in low light when the pupils are dilated. There is difficulty with daytime driving and reading.

Box 5.45 Three cardinal features of primary open-angle glaucoma

1. Raised intraocular pressure > 21–22 mmHg (> 30 mmHg warrants urgent referral to an ophthalmologist)
2. A cupped optic disc with an increased cup–disc ratio
3. Visual field loss

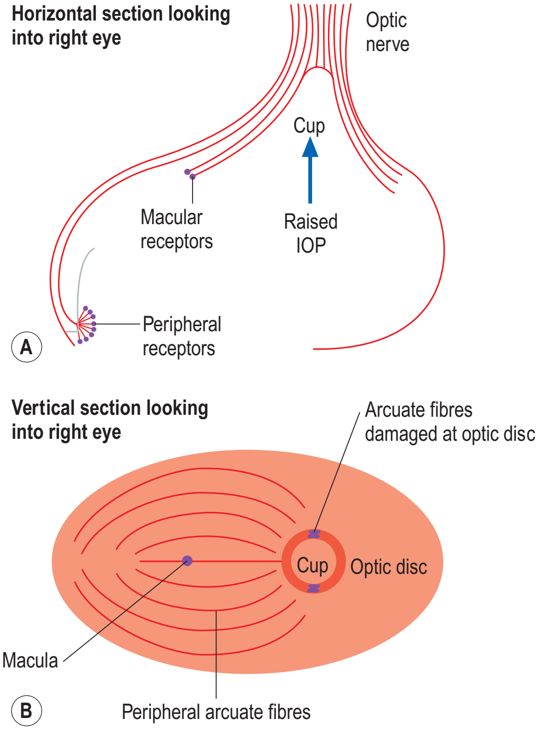

Horizontal section looking into right eye
Optic nerve
Cup
Macular receptors
Raised IOP
Peripheral receptors
A
Vertical section looking into right eye
Arcuate fibres damaged at optic disc
Cup
Optic disc
Macula
B
Peripheral arcuate fibres

Figure 5.81 Cupping of the optic disc and arcuate scotoma in primary open-angle glaucoma. IOP, intraocular pressure.

arcuate scotoma. Patients may start bumping into things.

Feedback to patient

There is certainly a degree of redness emanating from the centre of the eye and I am concerned about the possibility of a condition called uveitis in which the front of the eye becomes inflamed. It can be associated with inflammatory bowel disease. I think we should ask an eye specialist to have a look at this now and consider what treatment might be best to settle it down. It is almost certainly unrelated to the cataracts or the glaucoma, both of which are very common conditions in their own right. I would not expect the uveitis to affect your vision if we can settle it down quickly. I'd be happy to go into more detail if you'd like me to, and answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has evident cataracts and also a history of glaucoma, although cupping of the disc or field defects cannot be accurately assessed because of the cataracts. He now also has bilateral red and painful eyes, with the redness close to the limbus.

Provide a diagnosis or differential diagnosis with supporting evidence

He almost certainly has uveitis, associated with inflammatory bowel disease. Acute glaucoma is not likely in someone with a background history of chronic glaucoma and is seldom bilateral. Keratitis and scleritis are conceivably possible causes.

Outline an investigation and management plan

He should see an ophthalmologist urgently. The uveitis may then be best settled by treating the inflammatory bowel disease and with topical steroids after careful eye examination. Once the uveitis is settling further assessment of his cataracts and chronic glaucoma will be possible although it will be important for his intraocular pressures to be checked now.

To treat his cataracts, routinely, phacoemulsification with lens implantation can be performed as day surgery and is increasingly 'sutureless'. Yttrium–aluminium–garnet (YAG) laser capsulotomy is also used to eradicate a posterior capsule opacity.

Endocrine problems

Examination of the thyroid

- Ask the patient to sit comfortably at the edge of the bed or on a chair. Stand back and observe, paying particular attention to the face.
- Look at the thyroid gland from the front. Note any scars indicating previous surgery.
- Ask whether there is any pain or tenderness, and then feel the thyroid gland from behind (Fig. 5.82). Be gentle, because thyroid examination can be uncomfortable for patients. Feel the isthmus, which overlies the thyroid cartilage, with your right middle and index fingers, and then feel the lobes. Note any diffuse goitre or area of focal nodularity. Note the gland's size and texture.
- Consider asking the patient to swallow a glass of water if you find a goitre, to see and feel whether it is readily mobile.
- Feel for lymph nodes – supraclavicular, submandibular, postauricular, suboccipital. If there are palpable nodes, note if they are separate and tender (reactive hyperplasia), hard and clustered together (carcinoma), soft and rubbery (lymphoma), mobile or fixed.
- Auscultate the thyroid gland bilaterally for bruits.
- Examine the eyes for those features in Box 5.47 (p. 844).
- Observe the face, skin and hair for signs of hyperthyroidism or hypothyroidism.
- Feel the pulse.
- Inspect the palms for erythema and feel for sweat. Note any clubbing. Note any tremor with the arms outstretched.
- Ask your patient to abduct their shoulders to assess for proximal muscle weakness.
- Look at the legs for pretibial myxoedema.
- Test the ankle reflexes.
- You will probably discover early in the course of the examination if you are dealing with a thyroid lump, hyperthyroidism or hypothyroidism, directing your assessment accordingly.

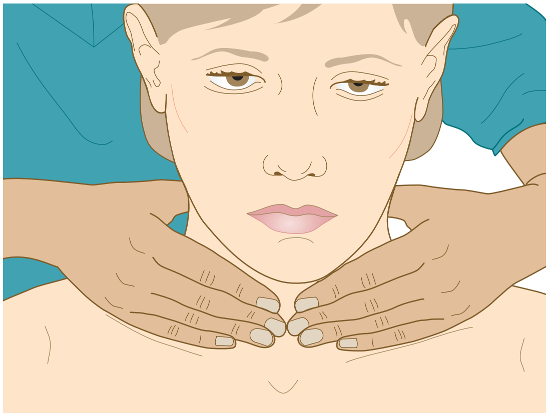


Figure 5.82 Examining the thyroid and thyroid status.

Summary

A summary of the thyroid/endocrine examination sequence is given in the Summary box.

SUMMARY BOX – THYROID/ENDOCRINE SYSTEM EXAMINATION

Examining the endocrine system in PACES will usually entail examining the thyroid (above), or the face and hands for diagnoses such as Cushing's syndrome or acromegaly.

Cases

CASE 5.31 HYPERTHYROIDISM, THYROTOXICOSIS AND GRAVES' DISEASE

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Mrs Angela Stapleton, aged 35 years

This woman has been admitted to the acute medical unit with tachycardia and tremor.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old woman admitted to the acute medical unit with tachycardia and tremor. Your general practitioner suspected an overactive thyroid and sent you in. You have also noticed weight loss and heat intolerance and experienced diarrhoea and generalised anxiety over the past few months. You have slight protrusion of the eyeballs with occasional redness. You are usually well. You are especially concerned because you have just discovered that you are pregnant.

Focused history and examination

Initial history

- Ask about symptoms of hyperthyroidism or thyrotoxicosis (Box 5.46).

Box 5.46 **Symptoms of thyrotoxicosis (of any cause)**

- Weight loss
- Increased appetite
- Heat intolerance
- Preference for cold and sweating
- Diarrhoea
- Tremor
- Hyperactivity, irritability, insomnia or anxiety
- Depression (especially elderly)
- Oligomenorrhoea and loss of libido
- Polyuria
- Weakness and fatigue

Initial examination

- Look for one or more of the triad of groups of signs.

1. Hyperthyroidism

The hands are *warm and sweaty* with *palmar erythema*. *Tremor* is often obvious (with the arms extended a piece of paper on the hands detects subtle fine tremors). There is *tachycardia* at rest (usually sinus tachycardia, may be atrial fibrillation). There may be *proximal muscle weakness*. These signs may occur in thyrotoxicosis of any cause. A *bruit* bilaterally over the thyroid is specific to *Graves' disease*.

2. Thyroid eye disease (TED)

TED has an autoimmune basis, with associated thyroid autoimmunity always detectable, probably reflecting shared autoantigens between the thyroid and the orbit. Most patients have concurrent thyrotoxicosis due to Graves' disease and the classic presentation is thyrotoxicosis, diffuse goitre and exophthalmos. Some patients develop TED in the months before becoming thyrotoxic, and occasionally it precedes thyrotoxicosis by years. Extraocular muscles, retro-ocular fat and connective tissue, eyelids and anterior periorbital tissues are affected by lymphocyte infiltration, inflammatory cytokine cascades and interstitial oedema, resulting in volume expansion. Graves' ophthalmopathy (Fig. 5.83) occurs clinically in around 60% of patients and is radiologically detectable in around 90%. TED signs are listed in Box 5.47.

3. Pretibial myxoedema

This is rare (1–2% of Graves' disease) but specific to Graves' disease. There are *elevated shin lesions* with

Box 5.47 **Signs of thyroid eye disease (TED)**

- Swelling and redness of the eyelids, periorbital tissues and conjunctiva (chemosis refers to corneal oedema)
- Proptosis (anterior displacement of the globe, best seen from above, standing behind the patient) resulting in exophthalmos – lower sclera visible between cornea and lower lid (lower or upper lid retraction refer to visible sclera between the cornea and the lid)
- Impaired lid closure and corneal ulceration, especially if levator muscle affected
- Moving your finger downwards quite fast and asking the patient to follow it, while fixing their forehead with your other hand, will elicit lid lag
- Note that lid retraction and lid lag are due to excess sympathetic activity and not specific to Graves' disease
- Ophthalmoplegia causing diplopia (often a complex ophthalmoplegia involving numerous ocular muscles)
- Visual loss due to compression of the optic nerve at the orbital apex (exophthalmos is not always present in this sight-threatening situation and does not correlate well with disease severity; indeed, patients with minimal exophthalmos may be at higher risk of optic nerve compression because displacement of the eye forwards helps to decompress the optic nerve)

Common early symptoms of TED included altered appearance, eye surface symptoms (grittiness, photophobia, lacrimation), diplopia (especially at extremes of gaze), blurred vision (due to tear film abnormalities, refractive problems or subtle extraocular palsy – but blurred vision that does not improve with blinking, refraction/pinhole or by occluding either eye may be due to optic nerve compression) and retro-orbital ache. The natural history of TED comprises an initial progressive phase lasting a few months before reaching a peak before it improves spontaneously. These changeable phases can last 1–2 years until a chronic, 'burnt-out' stage is reached when no further change is likely. Atypical features requiring orbital imaging include unilateral disease, no evidence of thyroid disease, absence of upper lid retraction, divergent strabismus, diplopia alone and diplopia that is worse towards the end of the day. The differential diagnosis includes myasthenia gravis, orbital myositis, chronic progressive external ophthalmoplegia, orbital tumours, carotid–cavernous fistula and any inflammatory orbitopathy (e.g. Wegener's granulomatosis).

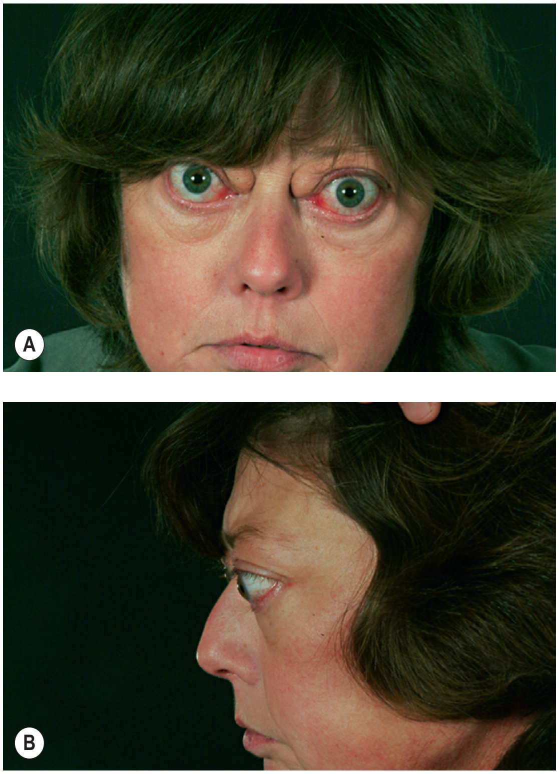


Figure 5.83 (A, B) Thyroid eye disease.

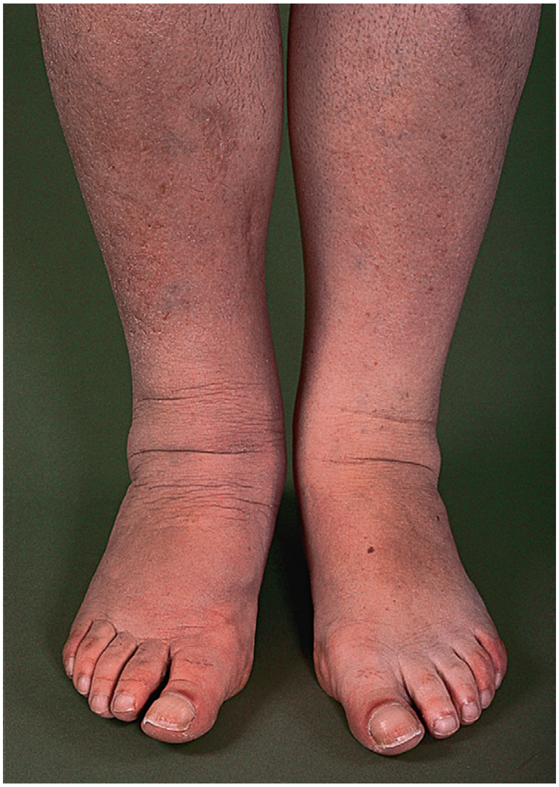


Figure 5.84 Pretibial myxoedema (note also acropachy).

well-defined edges (Fig. 5.84). Lesions may be *nodular or plaque-like, purplish red or brown* and the *skin is shiny*, with a *thickened, orange-peel appearance*. Lesions can occur at other sites. They are usually painless. Coarse hairs tend to occur in the vicinity. Look also for thyroid acropachy (clubbing) and onycholysis (Plummer's nails), which affect a small minority of patients.

Further assessment

- Be aware that thyrotoxicosis and hyperthyroidism are not synonymous (Box 5.48) and consider the causes of thyrotoxicosis (Table 5.43).
- Explore concerns.

Box 5.48 **Thyrotoxicosis and hyperthyroidism**

- Thyrotoxicosis is the clinical syndrome that arises from excessive circulating thyroid hormone levels and is usually caused by Graves' disease or toxic nodular thyroid disease, both of which are forms of hyperthyroidism
- Hyperthyroidism is the term for overactive tissue within the thyroid gland that causes an overproduction of thyroid hormones
- Hyperthyroidism is thus a cause of thyrotoxicosis, but hyperthyroidism and thyrotoxicosis are not synonymous and, for instance, thyrotoxicosis could be caused by ingestion of exogenous thyroid hormone or destructive thyroiditis causing release of stored hormone

Feedback to patient

All of your symptoms are very suggestive of an overactive thyroid gland. The eye problems can also be caused by this. We should aim to confirm this diagnosis with blood tests and then settle things down with treatment. In terms of treatment we could firstly settle down the immediate symptoms with medication (beta blockers) and then get expert advice on treating the problem in the longer term; options usually include tablets or a radioactive treatment to the thyroid gland, and occasionally surgery. Most patients will settle with the more straightforward of the options, though the best treatment is determined by a number of considerations, not least pregnancy. In pregnancy drugs treatment is going to be the safest option and the condition can be managed very effectively but best under the supervision of a specialist in thyroid problems. I'd be happy to answer any further questions or concerns that you may have.

Table 5.43 Causes of thyrotoxicosis

	Disease	Causes	Distinguishing features
Primary hyperthyroidism	Graves' disease	Thyroid-stimulating IgG antibodies are TSH receptor antibodies that bind to and stimulate the TSH receptor	Painless diffuse goitre in > 90% Ophthalmopathy Pretibial myxoedema
	Toxic nodular thyroid disease (toxic multinodular goitre)	Unknown	Painful goitre Most common cause in older people
	Toxic adenoma	Solitary secreting adenoma	Thyrotoxicosis without goitre
	Other	Metastatic thyroid cancer	Rare Consider if above three causes not confirmed
		Genetic	
		Ectopic thyroid tissue	
Secondary hyperthyroidism	TSH-secreting pituitary adenoma		Possibly part of wider pituitary disease TSH detectable despite high FT4 and FT3
	Gestational thyrotoxicosis		Hyperemesis gravidarum due to high levels of human chorionic gonadotrophin in first trimester, which stimulates the TSH receptor
	Thyroid hormone resistance syndrome		Thyrotoxicosis uncommon Elevated FT4 and FT3 due to peripheral resistance to action
Thyrotoxicosis without hyperthyroidism	Destructive thyroiditis	Subacute (De Quervain's)	Viral Small, tender goitre High ESR Initial thyrotoxicosis without hyperthyroidism due to release of stored hormone Hypothyroidism within weeks Recovery over 3–6 months May respond to steroids
		Postpartum thyroiditis	Similar to viral thyroiditis but goitre painless
		Drug-induced (amiodarone, lithium, other drugs inducing autoimmunity or inflammatory thyroiditis)	Onset abrupt
	Excess thyroid hormone ingestion		History

ESR, erythrocyte sedimentation rate; FT3, free tri-iodothyronine; FT4, free thyroxine; IgG, immunoglobulin G; TSH, thyroid-stimulating hormone.

Feedback to examiners

Summarise the key history and examination findings

This woman has numerous symptoms and signs of hyperthyroidism with thyrotoxicosis, a diffuse goitre and exophthalmos.

Provide a diagnosis or differential diagnosis with supporting evidence

She almost certainly has Graves' disease.

Outline an investigation and management plan

Thyroid function tests are needed [Table 5.44]. Serum autoantibodies against thyroglobulin and thyroid peroxidase are present in 80% of patients with Graves' disease but also in many healthy people, especially women (peroxidase is an enzyme needed for thyroid hormone synthesis). Thyroid-stimulating hormone receptor-stimulating antibodies are not widely available, but diagnosis of Graves' disease is usually clinical.

Thyroid scintiscanning with technetium-99m or iodine-131 is useful when thyrotoxicosis without

Table 5.44 Interpreting thyroid function tests (TFTs)

FT4/FT3	TSH	Interpretation
Normal	Normal	Normal
↑	↓	Primary hyperthyroidism and thyrotoxicosis (Table 5.43)
↓	↑	Primary hypothyroidism
Normal	↓	Subclinical hyperthyroidism* Recent treatment for hyperthyroidism Drug induced (e.g. corticosteroids or dopamine) Non-thyroidal illness (uncommon pattern)
Normal	↑	Subclinical hypothyroidism Poor compliance with thyroxine replacement treatment Malabsorption of thyroxine Assay interference Drugs (e.g. amiodarone, especially early stage) Non-thyroidal illness (recovery stage) TSH resistance
↓	Normal or ↓	Non-thyroidal illness (commonest pattern in non-thyroidal illness); reason uncertain (? altered hypothalamic function, thyroid binding capacity, uptake of T4, conversion of T4 to T3) Central hypothyroidism Isolated TSH deficiency
↑	Normal or ↑	Assay interference Thyroxine replacement treatment (including poor compliance) Drugs (e.g. amiodarone, heparin) Non-thyroidal illness TSH-secreting pituitary tumour Resistance to thyroid hormone

Background information

Thyroid hormones have a diverse range of roles in metabolism and development. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates release of thyroid-stimulating hormone (TSH) from the anterior pituitary, which in turn directs production of and release of T4 and T3. T4 is the major hormone released from the thyroid, subsequently converted to biologically active T3. The hypothalamic–pituitary–thyroid axis maintains levels of circulating T4 and T3 within relatively tight limits through compensatory alterations in TRH and TSH secretion such that TSH is usually a sensitive indicator of thyroid status and an ideal initial screening test for thyroid disturbance. T4 and T3 are unsuitable as a screening test as they may be maintained within normal limits by TSH in subclinical hypothyroidism or subclinical hyperthyroidism, but T4 or T3 (or sometimes both) should be checked if TSH is abnormal. Total T4 or T3 (TT4, TT3) levels are unsuitable, as alterations in thyroid hormone-binding carrier proteins such as thyroid-binding globulin and albumin may affect measurement of TT4 or TT3 levels; for example, oestrogen can increase levels of thyroid-binding globulin. Thus, free T4 or T3 (FT4 or FT3) levels should always be used. Checking TSH alone may be misleading in a small number of situations including non-thyroidal illness, recent treatment for hyperthyroidism, central hypothyroidism (hypothalamic or pituitary disease), a TSH-secreting adenoma or resistance to thyroid hormone. Interpretation of TFTs is usually straightforward, the combined measurement of TSH with T4 or T3 usually enabling a diagnosis of hyperthyroidism or hypothyroidism to be made. A small number of results offer confusion. A guide to interpreting TFTs is given here.

*Subclinical hyperthyroidism is suggested by a depressed TSH and high-normal or slightly elevated FT3 or FT4, in the absence of overt symptoms; anxiety or sleep disturbance may be present. Over time, many such patients do develop more pronounced hyperthyroidism. The decision to treat is often determined by a wish to improve subtle symptoms unmasked by closer enquiry, especially if biochemical progression is occurring. Atrial fibrillation is a compelling reason to treat, since it is about three times more common in people with 'subclinical' hyperthyroidism. A small dose of carbimazole, such as 5–10 mg daily, may suffice, indicated if TSH is consistently < 0.1 mU/l. Radioiodine may be used.

hyperthyroidism is suspected, because isotope uptake is low or absent compared with all types of hyperthyroidism in which it is high. It can identify a toxic adenoma by demonstrating uptake in the adenoma with complete suppression of uptake in the rest of the gland. Such hot spots are important to identify as they are less responsive to carbimazole.

Treatment of hyperthyroidism [Box 5.49] may be with antithyroid drugs (carbimazole) to inhibit thyroid hormone production via peroxidise, and beta blockers to relieve symptoms. Radioactive iodine (^{131}I) acts slowly but is very effective; contraindications include pregnancy, lactation and active ophthalmopathy. Indications for subtotal thyroidectomy include a large goitre and relapse. Hypothyroidism is a common side effect of treatment. Management of thyroid eye disease includes avoiding smoking, corneal lubricants and steroids.

Graves' disease is significant in pregnancy because thyroid-stimulating hormone receptor-stimulating antibodies can cross the placenta and cause fetal hyperthyroidism and tachycardia. Antithyroid drugs can also cross the placenta and cause fetal hypothyroidism. Where necessary, the lowest possible dose is used. Breastfeeding is possible with a low-dose titration regimen. For all of these reasons this woman should be treated and monitored by an expert endocrinologist.

Box 5.49 **Treatment of thyrotoxicosis**

Distinguishing the cause of thyrotoxicosis is an essential initial step in management, once the diagnosis has been confirmed biochemically. In particular, antithyroid drug treatment can cure around 50% of patients with Graves' disease, will only control but not cure nodular thyroid disease, and is useless in destructive thyroiditis. Radioiodine is generally used to treat patients with toxic nodular goitre and Graves' disease that has relapsed, but caution is necessary in those patients with ophthalmopathy and pregnancy and breastfeeding are absolute contraindications. Special care is needed in the management of Graves' disease in pregnancy; the lowest dose of antithyroid drug should be used and measurement of thyroid-stimulating hormone (TSH) receptor antibodies in the mother can be used to predict the likelihood of the fetus developing neonatal hyperthyroidism.

Antithyroid drugs

Antithyroid drugs, such as carbimazole and propylthiouracil, inhibit iodide organification by thyroid peroxidase, reducing T3 and T4 production. They also reduce TSH receptor-stimulating antibody levels. Carbimazole is most widely used and patients should be warned about symptoms of infection and rashes; the earliest symptom of incipient agranulocytosis is usually a sore throat but fever or mouth ulcers are also common and patients should stop treatment and seek an urgent full blood count. Neutropenia occurs in around 0.1% of patients. More common side effects include rash, fever and cholestasis. Carbimazole may be started in one of two main regimens:

Titration or reducing regimen

30–60 mg of carbimazole is taken daily in three or four divided doses, reduced over 4–8 weeks as the patient becomes euthyroid and guided by free thyroxine (FT4) levels, usually to 5–15 mg daily.

Block–replace regimen

40 mg carbimazole is taken daily and maintained, adding T4 when the patient becomes euthyroid, usually at around 1 month. Fewer clinic visits are required and biochemical control is often smoother. Treatment is usually continued for 18–24 months, but around half of patients will eventually relapse when it is discontinued.

Beta blockers

Carbimazole takes about a month to improve thyroid status. Symptom control is achieved in the interim with non-cardioselective beta blockers (e.g. propranolol 80 mg thrice daily, weaning to 40 mg twice daily over 4–6 weeks and ceased once carbimazole has taken effect).

Radioactive iodine

Radioactive iodine (^{131}I) acts slowly, and is very effective, but can cause early transient hypothyroidism, and later permanent hypothyroidism at a rate of around 10% in the first year and a small percentage increase per year thereafter. It can also cause transient thyroiditis, and although antithyroid drugs can be used to reduce this they increase the need for higher doses of ^{131}I. Lifelong thyroxine replacement is often needed after treatment. Contraindications to ^{131}I include pregnancy, lactation and active ophthalmopathy. Patients with ophthalmopathy should be offered corticosteroids following ^{131}I to reduce the risk of exacerbation of eye disease. ^{131}I is the treatment of choice for toxic multinodular goitre, except for large goitres and those with retrosternal extension requiring surgery.

Surgery

Surgery is now much less commonplace given the efficacy and safety of radioiodine but indications for subtotal thyroidectomy in Graves' disease may include a large goitre, disease relapse and situations in which ^{131}I is contraindicated, unavailable or unacceptable to the patient. Hypothyroidism is a common side effect.

Thyrotoxic crisis or 'storm'

This is uncommon, but has a mortality of around 50% and should be recognised and treated urgently. Treatments include propylthiouracil 600 mg then 200 mg 6-hourly, stable iodine (Lugol's iodine) at least 1 hour later, propranolol 60 mg 4-hourly, dexamethasone and intravenous fluids. Precipitating causes include thyroid surgery, radioiodine, withdrawal of drugs and acute illness.

Monitoring treatment

Thyroid function tests should be checked annually if stable, and after 2 months following any dose adjustment. It takes several weeks for results to reflect changes in treatment.

Thyroid eye disease (TED)

Ensuring there are no sight-threatening complications – corneal ulceration or optic neuropathy – is a first consideration. Corneal lubricants (artificial teardrops, especially gels and ointments such as hypromellose eye drops, Viscotears gel and Lacri-Lube ointment) offer corneal protection and symptom relief. Smoking increases the risk of developing TED by seven- to eight-fold and cessation is essential. Correcting thyroid dysfunction is usually followed by improvement of eye symptoms over several months. A small risk of exacerbation of TED has been reported after radioiodine, especially in smokers, whilst antithyroid drugs and thyroidectomy seem to be neutral. Radioiodine may be administered once TED is inactive or earlier with a short course of steroids. The main medical treatment is steroids. Pulse therapy with intravenous methylprednisolone (initially 500–1000 mg weekly, for 10–12 weeks) is more beneficial than oral steroids. Orbital irradiation may consolidate the effects of steroids. Either treatment is only effective in active TED. Surgery may have a role in all phases of TED. Patients with optic neuropathy who do not respond to or who cannot tolerate steroids must be considered for urgent orbital decompression. Rehabilitative reconstructive surgery may be considered once TED is inactive. Prisms (special lenses fitted to spectacles to refract light and thus achieve binocular vision when eyes are misaligned) are helpful in diplopia. Rituximab (humanised mouse monoclonal antibody to CD20) may have a role. TED should be referred urgently to specialists (European Group on Graves' Orbitopathy recommendations) if there is visual loss or change in intensity or colour, a corneal opacity, inability to close the eyes fully to cover the cornea or a swollen optic disc. Other troubling or progressive problems should be referred electively.

CASE 5.32 HYPOTHYROIDISM

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Mrs Marjorie Dawe, aged 70 years
>
> This woamn has been admitted to the acute medical unit with a possible non-ST elevation myocardial infarction and is stable but reports to the doctor that she has become extremely tired in the past few months.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old woman admitted to the acute medical unit with a possible non-ST elevation myocardial infarction. You are now stable. You have also noticed extreme tiredness, weight gain and cold intolerance and experienced constipation and mood change over the past few months. You are usually well, but you are always so tired and wish you could have more energy.

Focused history and examination

Initial history

- Ask about symptoms of features of hypothyroidism (Box 5.50).

Box 5.50 Symptoms of hypothyroidism

- Tiredness / exhaustion / somnolence
- Weight gain
- Preference for warmth / intolerance of cold
- Mood change including depression, or slow cognition
- Constipation
- Menstrual disturbance including menorrhagia
- Myalgia, especially calf discomfort and stiffness
- Carpal tunnel syndrome
- Hearing impairment

Initial examination

- You may miss hypothyroidism and think, 'just another little old lady'. Many of the clinical features are non-specific and insidious. They include *excess weight, myxoedematous facial features* (*thick and coarse, with periorbital oedema* – puffiness especially below the eyes, and sometimes *hoarseness*), *dry skin, and fine, brittle hair with loss of the outer eyebrows* (Fig. 5.85). There may be *delayed relaxation of ankle and other deep tendon reflexes*.

Further assessment

- Consider the possible causes of hypothyroidism (Box 5.51). The commonest cause in developed countries is autoimmune thyroiditis, which may be associated

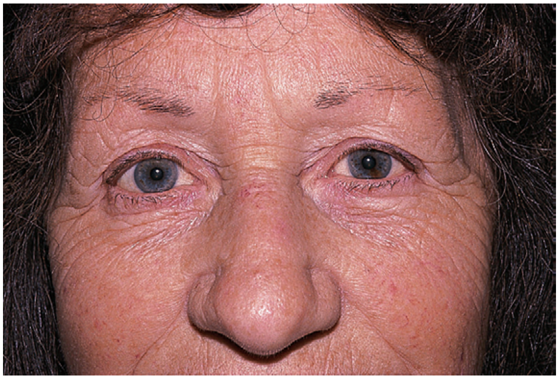


Figure 5.85 Hypothyroidism.

Box 5.51 Causes of hypothyroidism

- Autoimmune Hashimoto's thyroiditis*
- Atrophic autoimmune thyroiditis
- Iatrogenic – thyroidectomy for hyperthyroidism or thyroid cancer, radioiodine therapy
- Destructive thyroiditis – painful subacute thyroiditis (also known as De Quervain's thyroiditis), silent thyroiditis, postpartum thyroiditis
- Iodine deficiency (in some parts of the world remains highly prevalent)
- Drugs – carbimazole, methimazole, propylthiouracil, iodine, amiodarone, lithium, interferons, thalidomide, sunitinib, rifampicin
- Congenital hypothyroidism – thyroid aplasia or hypoplasia, defective biosynthesis of thyroid hormones
- Disorders of the pituitary or hypothalamus (secondary hypothyroidism)

*Hashimoto's thyroiditis is the commonest cause of hypothyroidism, in which dense lymphocytic infiltration of the thyroid gland produces a diffuse or finely micronodular goitre. It typically affects middle-aged and older women, presenting with hypothyroidism, goitre, or both and is autoimmune. Associated conditions include vitiligo, pernicious anaemia, type 1 diabetes, Addison's disease and premature ovarian failure.

with goitre (Hashimoto's thyroiditis) or, with equal frequency, thyroid atrophy.

- Be aware of serious complications of severe hypothyroidism – serous effusions (pleural, pericardial, peritoneal, joint), heart failure, bradycardia, dyslipidaemia (raised total cholesterol and low-density lipoprotein with increased cardiovascular disease risk), anaemia (iron deficiency, macrocytic, pernicious, normochromic, normocytic), cerebellar dysfunction, psychiatric manifestations, and impaired consciousness (myxoedema coma).
- Explore concerns.

Feedback to patient

All of your symptoms are very suggestive of an underactive thyroid gland. We should aim to confirm this diagnosis with blood tests and then settle things down with treatment. This is a very common condition and treatment is usually successful with a small dose of medication. One thing for us to consider, especially if this turns out to be a small heart attack, is cholesterol levels since an underactive thyroid can provoke high cholesterol levels. You will of course be feeling under the weather as a result of the heart attack but it is very likely that an underactive thyroid has been making you feel chronically tired and hopefully treatment would help this. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has numerous symptoms and signs of hypothyroidism.

Provide a diagnosis or differential diagnosis with supporting evidence

Hashimoto's thyroiditis would be the most likely cause.

Outline an investigation and management plan

Thyroid function tests are needed [Box 5.52] with a view to treatment [Box 5.53]. Diagnosis of primary hypothyroidism is confirmed by an increase in serum thyroid-stimulating hormone (TSH) concentration. If the cause is autoimmune, circulating antibodies directed at thyroid peroxidase (formerly known as microsomal antibodies) or thyroglobulin are

Box 5.52 **Thyroid function tests in hypothyroidism**

- Adults presenting with symptomatic hypothyroidism often have a thyroid-stimulating hormone (TSH) level > 10 mU/l, coupled with reduced serum free or total thyroxine (T4) concentration.
- Some have less severe hypothyroidism, with a serum TSH typically between 5 mU/l and 10 mU/l but a serum T4 concentration within the reference range; this is termed subclinical or mild hypothyroidism and in many patients represents a state of compensated or mild thyroid failure.
- Around 30% diurnal variation occurs in TSH levels, with a trough around 14.00 h, rising during the hours of darkness; this variability is conserved in mild hypothyroidism. Small variability also exists between assays for measuring TSH and reference ranges used by laboratories.
- Serum tri-iodothyronine (T3) concentration is often normal even in severe hypothyroidism because of increased conversion of T4 to T3, and is not a helpful investigation.
- Hypothyroidism secondary to hypothalamic or pituitary disease is associated with low TSH.

Box 5.53 **Treatment of hypothyroidism**

When to treat

Treating hypothyroidism is generally considered straightforward and mostly carried out in primary care; however, up to 50% of patients are overtreated or undertreated and a small but significant proportion of patients continue to feel unwell despite optimum treatment.

Overt hypothyroidism with thyroid-stimulating hormone (TSH) > 10 mU/l

Symptomatic people with TSH concentrations > 10 mU/l should be treated. Except in drug-induced hypothyroidism or the recovery phase of thyroiditis there is little chance of spontaneous recovery; treatment is therefore lifelong. TSH levels should be confirmed on a second sample. Adults with symptoms usually feel better treated, and treatment may also reverse dyslipidaemia and so benefit vascular risk.

Subclinical (mild) hypothyroidism: TSH between 5 and 10 mU/l (free serum thyroxine (T4) in reference range)

Treatment of subclinical hypothyroidism with levothyroxine is controversial. A 20-year follow-up study showed only small risk of progression to overt hypothyroidism, correlating with TSH levels and the presence of thyroid peroxidase antibodies. Some meta-analyses have shown links between subclinical hypothyroidism and cardiovascular morbidity and mortality but studies have failed to show benefit from levothyroxine replacement and it remains unclear as to whether vascular risk can be ameliorated by early thyroid hormone replacement. Further, in people aged more than 85 years, evidence suggests that subclinical hypothyroidism is associated with longevity. An expert panel did not support routinely treating subclinical hypothyroidism. In practice the TSH level should be re-measured, along with testing for thyroid peroxidase antibodies, within 3 months of the initial test to ascertain the persistence of the abnormal TSH and the tempo of thyroid failure. If there are symptoms consistent with hypothyroidism and the increased TSH persists, a therapeutic trial of levothyroxine for 3–6 months is reasonable. If the patient feels better – a third to half do – it is reasonable to continue treatment. If there are no symptoms and the TSH level seems stable with thyroid peroxidase antibodies present, the risk of progression to overt hypothyroidism is just under 5% per year and yearly TSH surveillance is satisfactory. If there are no symptoms and the TSH level seems stable with thyroid peroxidase antibodies absent, the risk of progression to

Box 5.53 **Treatment of hypothyroidism—cont'd**

overt hypothyroidism is around 2% per year and TSH surveillance every 3 years is recommended. In pregnancy, or in someone trying to conceive, mild hypothyroidism should always be treated.

Symptoms of hypothyroidism but normal TSH

Although a normal TSH level excludes primary hypothyroidism, without a serum free T4 assay secondary hypothyroidism from pituitary or hypothalamic disease cannot be excluded. Secondary hypothyroidism is almost always associated with other hormone deficiencies and clinical clues, e.g. low gonadotrophin levels in a postmenopausal woman, amenorrhoea, galactorrhoea, erectile dysfunction. Because of the possibility of secondary adrenal failure, full evaluation of pituitary function is important before starting levothyroxine in secondary hypothyroidism.

How to treat

Levothyroxine is the treatment of choice. Although commonly titrated upwards from 25 to 50 μg daily, this is unnecessary for most patients who may receive full replacement of 75 or 100 μg from the outset. Exceptions are those aged more than 60 years or those with ischaemic heart disease. The dose requirement depends on lean body mass, a daily dose of 1.6 μg/kg body weight rendering most patients euthyroid. This equates to 100 μg daily for a 60 kg woman and 125 μg daily for a 75 kg man. Combination therapy (T3 tri-iodothyronine with T4 levothyroxine) for primary hypothyroidism is not beneficial.

Monitoring treatment

Serum TSH measurement is used to monitor treatment except in pituitary disease. In longstanding untreated hypothyroidism there is pituitary thyrotroph hyperplasia, so TSH levels commonly take 3–6 months to fall into the reference range, even with full-dose levothyroxine. After starting levothyroxine, TSH and free T4 levels should be measured at 8–12 weeks with dose adjustments made accordingly. Measuring TSH annually is sufficient for those on a stable dose of levothyroxine. Pregnancy, to a lesser extent oestrogen use, and large changes in body weight lead to more unpredictable TSH fluctuations. Dose requirements for levothyroxine tend to decrease with age with reduced clearance of T4 and reduced body mass.

The target TSH level

The aim of levothyroxine treatment is symptom improvement, and the dose should usually be adjusted to maintain TSH levels within the lower half of the reference range, around 0.4–2.5 mU/l. If a patient feels perfectly well with a level in the upper half of the reference range, adjustment is unnecessary. If persistent fatigue, somnolence, or subtle cognitive problems persist then it is reasonable to increase the dose by 25 μg daily, or on alternate days. A fully suppressed serum TSH level (< 0.1 mU/l) should be avoided and is not associated with improved well-being, although a low level (0.1–0.4 mU/l) may be acceptable in a younger person. Low TSH levels in older people (> 60 years) should trigger a small dose reduction of 25 μg daily, or on alternate days since low levels of TSH (0.1–0.4 mU/l) increase the risk of osteoporosis and may contribute to increased risk of atrial fibrillation.

A persistently raised TSH level despite levothyroxine replacement

Four possibilities should be considered:

1. *Non-concordance with levothyroxine therapy*. Larger doses of levothyroxine than 150 μg daily are seldom necessary. It has a half-life of 7 days in the bloodstream and, if one tablet is missed, there will be no noticeable effect. In most people it is safe to recommend a double dose on the day after a missed tablet (exceptions being active ischaemic heart disease and atrial fibrillation). Taking levothyroxine weekly (seven times the daily dose taken once a week) is a safe regimen. Levothyroxine should be taken on an empty stomach to maximise absorption.
2. *Drugs*. Some drugs prevent absorption of levothyroxine (calcium salts, ferrous sulphate, aluminium hydroxide, cholestyramine). Some drugs increase clearance of levothyroxine (phenytoin, carbamazepine, phenobarbitone, rifampicin).
3. *Malabsorption*. Coeliac disease and autoimmune gastritis should be considered.
4. *Interference with laboratory assay*. The presence of heterophil antibodies can lead to artefacts.

Persistence of symptoms despite a well-controlled TSH level (0.1–2.5 mU/l)

It may take several months before symptoms of hypothyroidism fully resolve (especially muscle weakness, stiffness, or cognitive defects) after biochemical correction. If symptoms persist, other diagnoses should be considered, as mild abnormalities of thyroid function are common and may be incidental. If a patient clearly reports feeling worse on levothyroxine, this suggests Addison's disease. Other autoimmune conditions, notably pernicious anaemia, may coexist with hypothyroidism. Sleep apnoea may have non-specific symptoms superficially similar to hypothyroidism (tiredness, weight gain, poor concentration), and these may have triggered testing of thyroid function. If the TSH level is over 1.5 mU/l, a small increment of 25 μg on alternate days should be considered or a change to nocturnal dosing, which may provide a subtle increase in absorption. Some people continue to feel symptoms despite adequate replacement and absence of other identifiable conditions.

Hypothyroidism in pregnancy

Maternal hypothyroidism in pregnancy is associated with adverse obstetric outcomes and long-term developmental sequelae. Specialist management is needed.

Myxoedema coma

This is an uncommon complication seen in older people, often precipitated by illness such as infection. Reduced consciousness and hypothermia are common, not necessarily with coma. Heart failure, hypotension, hypoventilation and hyponatraemia also occur. Treatment is supportive, with intravenous fluids, slow re-warming, ventilation, antibiotics and intravenous T3 followed by oral or nasogastric T4 once improving. Hydrocortisone is given if hypoadrenalism is also possible.

Screening

Routine screening for thyroid disease is not recommended except for patients with Down's syndrome and Turner's syndrome, patients taking certain drugs (e.g. amiodarone, lithium, thalidomide, interferons, sunitinib, rifampicin), patients who have received radioiodine treatment or neck radiotherapy, patients who have had subtotal thyroidectomy and patients with type 1 diabetes and autoimmune Addison's disease.

detectable in over 90% and about 70% of patients, respectively.

Hypothyroidism in older patients and those with ischaemic heart disease should always be managed with caution. Because longstanding hypothyroidism may cause bradycardia, which can mask substantial asymptomatic coronary artery disease, levothyroxine should be replaced cautiously in patients over 60 years or those with known ischaemic heart disease. Particular caution is needed in profound and longstanding hypothyroidism (TSH > 50 mU/l). Here, or in active angina or following a recent acute coronary syndrome, the starting dose of levothyroxine should be 12.5 or 25 μg daily, increased every 3–6 weeks until euthyroidism is achieved.

CASE 5.33 GOITRE AND NECK LUMPS

Candidate information

Role

You are a doctor from the medical ward.

Scenario

Re: Mrs Sue Richards, aged 40 years

This woman was admitted to the orthopaedic ward for a carpal tunnel release operation. She mentioned to the orthopaedic doctors that she has a swelling in her neck and they have asked for the opinion of a physician. You were asked by your consultant to assess the suspected swelling in her neck.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 40-year-old woman on the orthopaedic ward and you mentioned to the admitting doctor that your neck seemed swollen. One of the medical doctors has been asked to see you about this. You are having a short admission to have surgery for carpal tunnel syndrome. You have not mentioned the neck swelling to a doctor before but your sister, who has an underactive thyroid, has been commenting on it for a few years. You do not have any of the symptoms your sister had when her thyroid was underactive. Indeed you feel well. Your weight is stable. Your skin and hair are normal. You do not seem to feel the heat or the cold any more than anyone else. Your bowel works normally. You do not have any problem with swallowing. You want to know why your neck seems swollen and whether there might be something wrong with your thyroid gland and what should be done.

Focused history and examination

Initial history

- Ask about symptoms of the neck lump. Most are asymptomatic and most are euthyroid (endocrine glands generally comprise much redundant tissue). Pressure symptoms (dysphagia, dysphonia, stridor) or pain (especially with bleeding into an adenoma) are possible.
- Ask about symptoms of hyperthyroidism and hypothyroidism (Cases 5.31 and 5.32).

Initial examination

- Note if there is a diffuse goitre, a multinodular goitre or a single thyroid nodule (Fig. 5.86).

Further assessment

- Consider causes (Box 5.54). The key issue is to exclude malignancy (Table 5.45) with further investigations.
- Explore concerns.

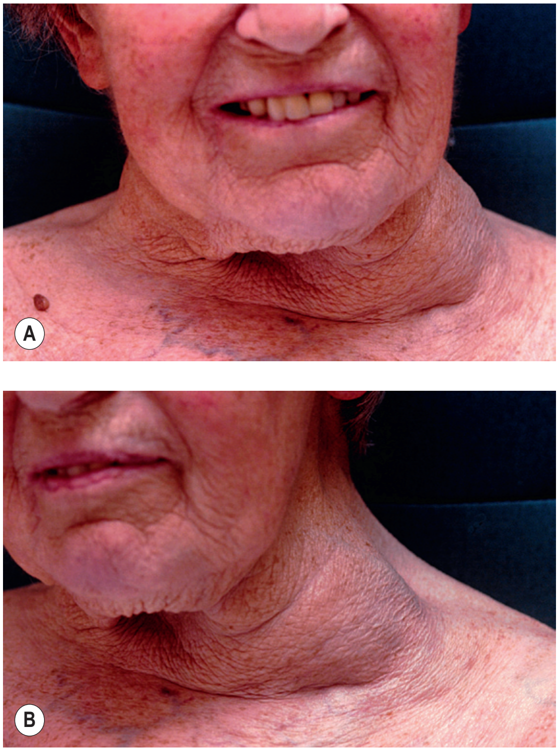


Figure 5.86 (A, B) Neck lump.

Box 5.54 Causes of a thyroid lump

Diffuse goitre

- Simple, non-toxic goitre
- Graves' disease
- Hashimoto's thyroiditis
- Subacute thyroiditis
- Lymphoma

Multinodular goitre

- Toxic multinodular goitre
- Hashimoto's thyroiditis

Single nodule

- Adenoma
- Cyst
- Carcinoma

Worldwide, iodine deficiency is a common cause of goitre.

Table 5.45 Thyroid malignancy

Papillary thyroid carcinoma	Most common Peak incidence young women Locally invasive Prognosis good if detected early
Follicular thyroid carcinoma	Peak incidence in older people Metastases more likely Prognosis still good if detected early
Hurthle cell carcinoma	Uncommon Poor prognosis
Anaplastic carcinoma	Peak incidence in older people Aggressive with high mortality
Lymphoma	Uncommon Good prognosis

Feedback to patient

You have a swelling of the thyroid gland, sometimes known as goitre. These swellings do not usually give rise to symptoms of an overactive or underactive thyroid but of course the swelling itself can be uncomfortable and we should aim to establish what has caused it and then treat it. Usually thyroid lumps are benign but occasionally not and I think we should arrange a thyroid scan in the first instance to assess it in more detail. We should also arrange some blood tests to make sure that the thyroid gland is not becoming overactive or underactive. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This lady has a thyroid lump, possibly an asymmetric or possibly a large single nodule.

Provide a diagnosis or differential diagnosis with supporting evidence

The possible causes are wide ranging and include a simple non-toxic goitre, Graves' disease, autoimmune thyroiditis, lymphoma or a large nodule.

Outline an investigation and management plan

She will require imaging to determine the nature of the mass and thyroid function tests to determine thyroid status. Thyroid lumps are common, often silent, and increasingly prevalent with age. Nodules may be solid, cystic, mixed (e.g. cystic degeneration within an adenoma) or calcified. The key issue is to exclude malignancy, although most thyroid lumps are benign. It is not possible without scanning to determine if a single palpable nodule is part of a multinodular thyroid. Measurement of size and exclusion of tracheal compression are best assessed by computed tomography or magnetic resonance imaging of the neck and thoracic inlet. Radionuclide imaging is less often used these days as it does not absolutely exclude malignancy, and although most cold nodules are benign and malignant nodules hot the latter may sometimes be cold. Fine-needle aspiration is the gold standard for diagnosis short of open excision. It is not possible to distinguish between a follicular adenoma and a follicular carcinoma on cytology and all follicular lesions should be excised. Indications for surgery include malignancy, concern about malignancy (e.g. large cysts are more likely to be malignant), continuing enlargement, pressure symptoms (dysphagia, dysphonia, stridor or pain) and cosmetic reasons.

CASE 5.34 HYPOPITUITARISM

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mr Graham Ellis, aged 76 years

This man is in the medical outpatient clinic. He has been feeling very tired over the past few months. Ten years ago he had radiotherapy to the pituitary gland for a benign condition.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 76-year-old man in the medical outpatient clinic. You have been feeling very tired over the past few months, and sometimes lightheaded, and have noticed generalised loss of body hair. Your family thinks that you have a pale, sallow complexion. Ten years ago you had radiotherapy to the pituitary gland for a benign condition. You wonder if this might be relevant.

Focused history and examination

Initial history

- Ask about hormone deficiency symptoms listed in Table 5.46. The anterior pituitary produces thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone, growth hormone, gonadotrophic hormones and prolactin. Posterior pituitary failure is much less common, and disorders of antidiuretic hormone (ADH) – syndrome of inappropriate ADH and diabetes insipidus – are discussed elsewhere.

Table 5.46 Symptoms and signs of hypopituitarism

Deficient hormone	Symptoms and signs	Tests of deficiency
Thyroid-stimulating hormone (TSH)	Fatigue Cold intolerance Weight gain Dry skin	Low TSH or thyroxine
Adrenocorticotrophic hormone (ACTH)	Fatigue Nausea and vomiting Weight loss Hypoglycaemia and hypotension (presyncope)	Low morning cortisol (< 100 nmol/l) with normal or low ACTH Hypoglycaemia Insulin-induced hypoglycaemia (failure to stimulate ACTH)
Growth hormone	Loss of well-being Altered body composition with increased fat mass and central fat Reduced muscle strength	Low insulin-like growth factor-1
Luteinising hormone (LH) and follicle-stimulating hormone (FSH)	Women – oligo/amenorrhoea, infertility, breast atrophy	Low estradiol with normal or reduced basal LH or FSH
	Men – loss of libido, erectile dysfunction, infertility, loss of body hair	Low testosterone with normal or reduced basal LH or FSH
Antidiuretic hormone	Diabetes insipidus	Water deprivation test (see Case 2.30)

Initial examination

Classic signs of hypopituitarism include *pallor*, *fine facial skin*, *decreased axillary and pubic hair*, *breast atrophy* in females and other signs of *hypogonadism*, reflecting the fact that gonadotrophins tend to be the early hormones lost. Hypopituitarism is shown in Figure 5.87.

Further assessment

Causes of hypopituitarism are listed in Box 5.55.

The three common secreting adenomas are outlined in Table 5.47, prolactinomas the most common. Non-functioning adenomas are also common. Rarer functioning adenomas secrete TSH or gonadotrophins. Adenomas are usually solitary and monoclonal, and in some activating mutations in G proteins have been identified as in many cases of acromegaly in which there is mutation of the G protein linking the growth-hormone-releasing hormone receptor to adenylate cyclase in growth hormone-secreting cells. Pituitary adenomas are sometimes part of multiple endocrine neoplasia. The four possible groups of ways in which a pituitary tumour might present are also outlined in Table 5.47.

Feedback to patient

> Your symptoms would suggest the possibility of an underactive pituitary gland, possibly but not necessarily contributed to by the previous

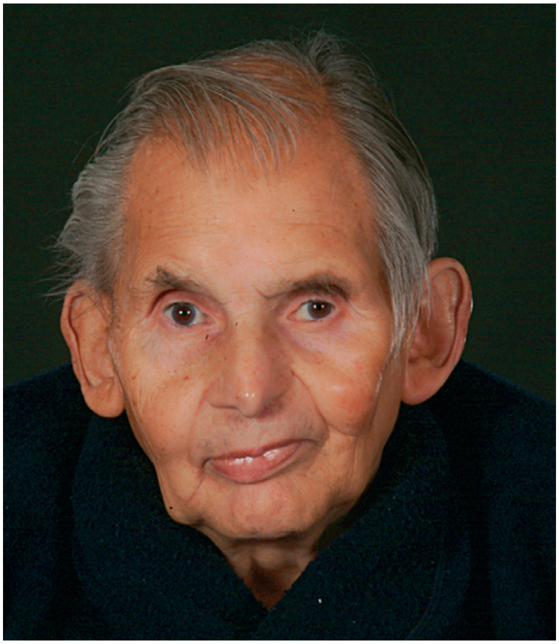


Figure 5.87 Hypopituitarism.

radiotherapy. The pituitary gland produces numerous hormones including hormones for stimulating body hair, a hormone for growth and well-being, thyroid hormone and a hormone to stimulate the adrenal gland without which we can become very lethargic and sometimes have low blood sugars. We should arrange blood tests to check the levels of all of these hormones, and a scan of the pituitary area, as well as seeking the advice of a hormone specialist/endocrinologist. We need to understand a little more about what is happening, but if there is a general lack of pituitary hormones then these can each be replaced with tablets. I'd be happy to answer any further questions or concerns that you may have.

Box 5.55 **Causes of hypopituitarism**

Pituitary adenoma

- Causes destruction or pressure on pituitary cells, especially macroadenoma

Other masses of the pituitary, sella or suprasellar cistern

- Craniopharyngioma
- Meningioma
- Metastases
- Cysts
- Aneurysm
- Optic glioma
- Granulomatous disease, e.g. sarcoidosis
- Infection

An enlarged sella filled with cerebrospinal fluid post-infarction, surgery or radiotherapy is known as empty sella syndrome.

Previous pituitary radiotherapy or surgery

Pituitary haemorrhage (apoplexy) or infarction

- e.g. Sheehan's syndrome – acute pituitary infarction due to hypovolaemia or septic shock as in meningococcaemia

Feedback to examiners

Summarise the key history and examination findings

This man has symptoms and signs suggesting insidious hypopituitarism.

Provide a diagnosis or differential diagnosis with supporting evidence

The likely cause is his previous pituitary radiotherapy with gradual atrophy.

Table 5.47 Presentations of pituitary adenomas

	Problem	Clinical presentation
Hormone overproduction	Prolactinoma (usually microadenoma in females, macroadenoma in males)	Hyperprolactinaemia
	Growth hormone secreting (macroadenoma)	Acromegaly
	Adrenocorticotrophic hormone secreting (microadenoma)	Cushing's disease
Consequence of size	Pituitary compression	Hypopituitarism
	Pituitary mass effect	Headache
	Suprasellar extension	Bitemporal hemianopia
		Stalk displacement – hyperprolactinaemia
		Hypothalamic damage
		Diabetes insipidus
		Hydrocephalus
Incidentaloma	No problem	Discovered during investigation for something else
Pituitary apoplexy	Acute haemorrhage from large adenoma	Acute severe headache and meningism – can present similarly to subarachnoid haemorrhage or meningitis Hypotension

Hyperprolactinaemia

Prolactin release from the anterior pituitary is normally inhibited by dopamine derived from the hypothalamus, but hyperprolactinaemia is a very common endocrine problem.

Table 5.47 Presentations of pituitary adenomas—cont'd

Problem	Clinical presentation
Causes	
Physiological – sleep, stress, pregnancy / lactation, nipple stimulation, sexual intercourse	
Pathological – pituitary tumour (prolactinoma often producing very high prolactin levels, mixed growth hormone / prolactin-secreting tumour); hypothalamic or pituitary stalk disease (mass compressing stalk causing 'disconnection hyperprolactinaemia', e.g. craniopharyngioma); infiltration, e.g. sarcoidosis; trauma; hypothyroidism (thyroid-releasing hormone stimulates prolactin as well as thyroid-stimulating hormone); polycystic ovarian syndrome, post seizure; idiopathic (likely covert microadenoma)	
Drugs (dopamine receptor antagonists, e.g. metoclopramide, neuroleptics, antidepressants, opiates, oestrogens, methyldopa, verapamil)	
Symptoms	
Hyperprolactinaemia can cause secondary hypogonadism via inhibition of gonadotrophin-releasing hormone and pituitary gonadotrophins; in women, galactorrhoea (always the result of hyperprolactinaemia and occurs in 90%), menstrual irregularity and infertility occur, whilst in men, who generally present later, there may be loss of libido, erectile dysfunction or reduced facial hair.	
Investigation	
Following confirmation of an elevated serum prolactin and exclusion of physiological and pathological causes, pituitary magnetic resonance imaging should be performed to investigate the presence of a prolactinoma or non-prolactinoma pituitary tumour. Macroprolactin is a polymeric form of prolactin, representing less than 5% of circulating prolactin and has limited bioavailability and bioactivity, but in patients with a raised prolactin level who lack the typical features of hyperprolactinaemia, macroprolactinaemia should be suspected and screened for.	
Treatment	
Cabergoline and bromocriptine are the two most commonly used dopamine agonists to normalise serum prolactin concentrations, restoring gonadal function and fertility. Both agents promote tumour shrinkage, even of large macroadenomas. Cabergoline is better tolerated than bromocriptine and has superior efficacy, although there are more safety data for bromocriptine. Both agents are considered safe in pregnancy. Surgery is seldom needed.	

Table 5.48 Pituitary hormone replacement

Deficient hormone	Treatment	Comments	
Thyroid-stimulating hormone	Thyroxine	Treated as for hypothyroidism	
Adrenocorticotrophic hormone	Hydrocortisone	Replaces missing glucocorticoid (much better than prednisolone or dexamethasone) Cortisol has short half-life so frequent dosing and small doses desirable Starting dose often 10 mg / 5 mg / 5 mg Increased dose needed during illness	
Growth hormone	Growth hormone	Subcutaneously in evening Improves body composition and quality of life (currently licensed only for severe deficiency)	
Gonadotrophins	Women – estradiol or conjugated oestrogens plus progesterone	Oral or transdermal	Sex steroids maintain normal body composition, bone mineral density and sexual function If fertility is desired in hypogonadotrophic hypogonadism, gonadotrophic releasing hormone may be used
	Men – testosterone	Intramuscular Transdermal Implant Buccal	
Prolactin	Not needed		
Antidiuretic hormone	Desmopressin	Intranasal Oral	

Outline an investigation and management plan

Diagnosis is by combined pituitary function testing and magnetic resonance imaging of the pituitary and sella region. The individual missing hormones should be replaced [Table 5.48].

CASE 5.35 ACROMEGALY

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

> Re: Mr Harold Ford, aged 55 years
>
> This man has been feeling generally unwell over the past few months, and noticed an increase in denture size.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 55-year-old man in the medical outpatient clinic. You have had symptoms for a few months (and maybe years when you think back as they have been so insidious) of fatigue, sweating, joint pains, headaches and a need for increasing sizes of shoes and dentures. You have also recently been diagnosed with early diabetes, which troubles you because your friend has diabetes and has to take insulin and has a multitude of problems. You wonder what might be wrong with you and what should be done.

Focused history and examination

Initial history

- Ask about symptoms of acromegaly. Some of the terms once used are rather old fashioned, even insulting ('spade-like hands'), and of little practical value. Newly diagnosed patients have often had symptoms for years, including increased sweating, increased size of shoes, gloves, rings or dentures, fatigue, joint pains and headaches. It typically becomes apparent between the ages of 40 and 60 years.

Initial examination

- Recognising acromegaly may be straightforward, although signs can be subtle as disease slowly and insidiously evolves. Examine the hands and face.

Face (Fig. 5.88A,B)

There are *prominent supraorbital ridges*. There is *prognathism* (protrusion of lower jaw), *soft-tissue enlargement of the nose, tongue and ears*. The *interdental distances are increased*. There is *general coarsening of features*. The voice may be husky.

Hands (Fig. 5.88C,D)

These are '*spade-like*', squared and large. The skin is *thick*, often with a rubbery texture and moist.

Further assessment

- Acromegaly is a rare, chronic, debilitating condition resulting from hypersecretion of growth hormone from a macroadenoma, which, if untreated, not only causes significant morbidity but also reduces life expectancy by about 10 years. Complications may be from the acromegaly itself or there may be symptoms arising from hypofunction of the compressed anterior pituitary such as hypogonadism or from local compressive symptoms (Table 5.49). State that you would check blood pressure and plasma glucose, and examine for bitemporal hemianopia.
- Explore concerns.

Feedback to patient

Your symptoms would suggest the possibility of a condition called acromegaly. The pituitary gland at the base of the brain produces numerous hormones including hormones for growth and well-being, and sometimes hormone production becomes overactive, sometimes as a result of a benign growth in the hormone production site. Acromegaly is the result of overproduction of growth hormone. We should arrange blood tests to check the levels of all your pituitary hormones, and a scan of the pituitary area, as well as seeking the advice of a hormone

Table 5.49 Complications of acromegaly

Complications of acromegaly itself	Hypertension
	Impaired glucose tolerance and diabetes
	Carpal tunnel syndrome
	Obstructive sleep apnoea
	Recurrent colorectal polyps and colorectal cancer
Anterior pituitary hypofunction	e.g. hypogonadism
Local compressive symptoms	Bitemporal hemianopia

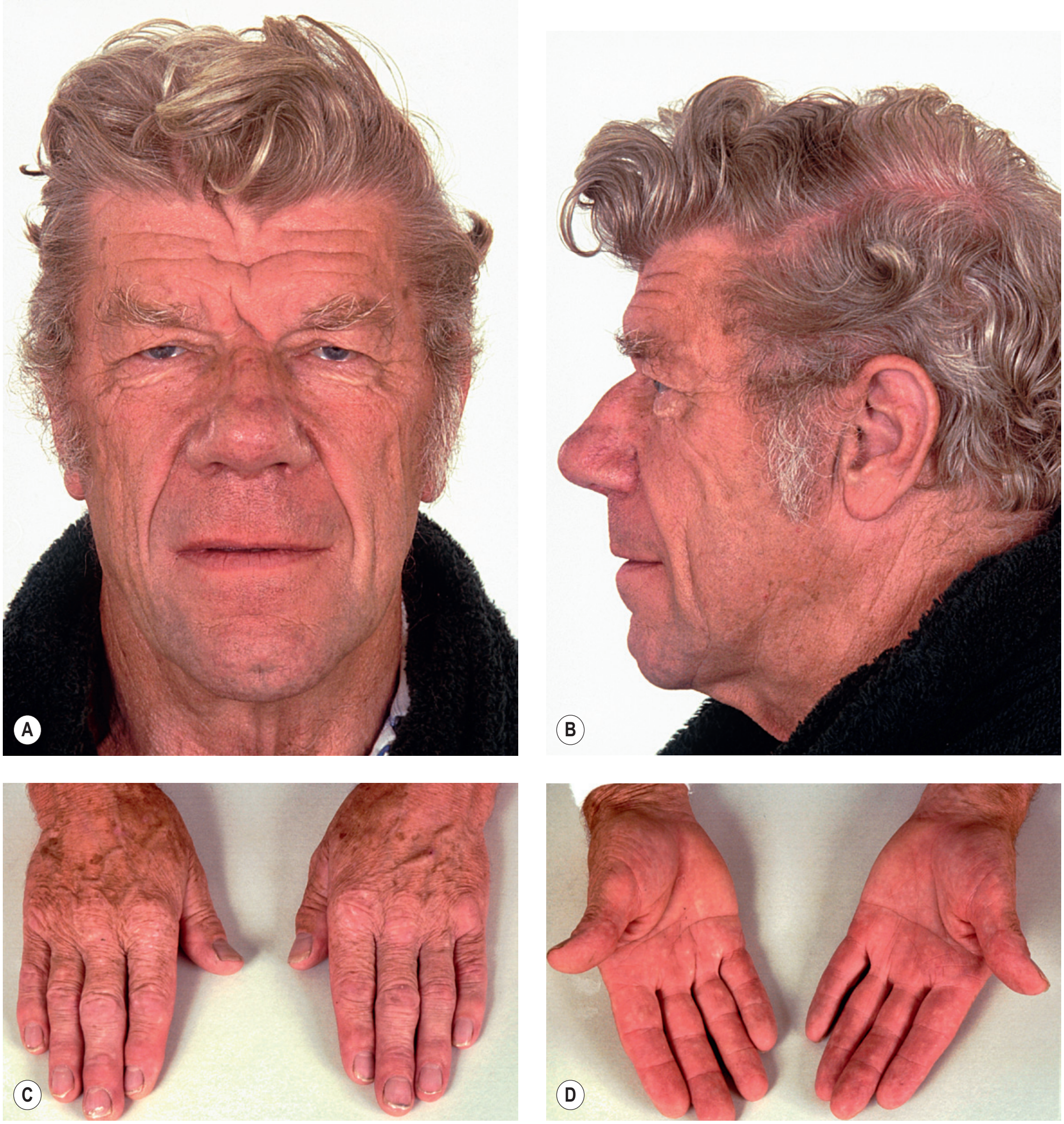


Figure 5.88 (A–D) Acromegaly.

specialist/endocrinologist. We need to understand a little more about what is happening first of all but if this does turn out to be acromegaly then various treatments are possible, from tablets and radioactive therapy to, in occasional circumstances, surgery. I should mention that diabetes is often caused by this condition and I would hope that in treating the underlying condition we might be able to avoid the diabetes becoming a problem. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has noticed increased sweating, increased size of dentures and fatigue. He has prominent supraorbital ridges, prognathism, soft-tissue enlargement of the nose, tongue and ears, and general coarsening of features. His hands are squared and large.

Table 5.50 Investigating acromegaly

Diagnosis	Serial growth hormone levels are unhelpful since secretion pulsatile and diagnosis is based on three key findings: 1. Clinical features 2. Failure of serum growth hormone to suppress to below 1 mU/l in a prolonged 75 g oral glucose tolerance test 3. Elevated serum insulin-like growth factor-1 level (mediates actions of growth hormone but influenced by many factors such as nutrition and disease)
Anterior pituitary function tests	Serum thyroid-stimulating hormone and thyroxine Serum cortisol Serum gonadotrophins and sex hormones (luteinising hormone releasing hormone, luteinising hormone, testosterone) Serum prolactin
Imaging	Magnetic resonance imaging (to assess size and regional anatomy in anticipation of surgery)
Complications	Electrocardiography Chest X-ray Sleep studies Colonoscopy (screening)

Provide a diagnosis or differential diagnosis with supporting evidence

He has typical features of acromegaly and possibly his diabetes is a complication of it.

Outline an investigation and management plan

Investigations to be considered in the diagnosis and assessment of acromegaly include levels of serum insulin-like growth factor-1, anterior pituitary function tests, imaging and assessment for complications [Table 5.50].

Successful treatment restores life expectancy to normal. Most patients proceed to trans-sphenoidal surgery (transcranial if significant suprasellar extension) by an experienced pituitary surgeon to remove the adenoma. Surgery is invariably complicated by early but transient diabetes insipidus. Larger adenomas may be difficult to completely excise, leaving patients with residual growth hormone excess. Most symptoms and signs of acromegaly do not regress after surgery, except those of disease activity such as sweating and oedema. Surgery remains the only hope of cure and surgical outcome varies widely with the size of the adenoma, which is related to the duration of the disease (90% versus 40–45% for microadenoma versus macroadenoma).

External pituitary radiotherapy alone can take 5–10 years to achieve growth hormone reduction and often ultimately induces hypopituitarism. It is a potential adjuvant therapy for patients with residual disease.

Medical control of acromegaly has improved significantly during recent years with the introduction of long-acting somatostatin analogues (effective in inhibiting secretion but tend not to cause significant tumour shrinkage) and pegvisomant (a very effective growth hormone receptor agonist, but which carries a small risk of hepatitis). Dopamine agonists such as cabergoline are generally ineffective.

CASE 5.36 CUSHING'S SYNDROME

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Marion Rowe, aged 52 years

This woman is in the medical outpatient clinic. She has been gaining weight and bruising easily.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 52-year-old woman who has recently put on a considerable amount of weight and noticed a tendency to thinning of skin, easy bruising and thigh muscle weakness. Recently your general practitioner diagnosed hypertension and 'mild' diabetes. You do not have any chronic diseases or take any medications. You are a former nurse and think you might have a condition called Cushing's syndrome, although you do not know much about this.

Focused history and examination

Initial history

- Ask about symptoms of Cushing's syndrome (Box 5.56).

Table 5.51 The three endogenous causes of Cushing's syndrome

		Cause	Features
Adrenocorticotrophic hormone (ACTH) dependent (80% of endogenous Cushing's syndrome)	Cushing's disease (80% of ACTH dependent Cushing's syndrome)	Pituitary microadenoma secreting ACTH	The most common non-iatrogenic cause, with typical features of Cushing's syndrome
	Ectopic ACTH	Often caused by a bronchial carcinoid or small-cell lung cancer	Ectopic ACTH secretion due to carcinoma usually of rapid onset with less florid signs of corticosteroid excess but significant weight loss, hypokalaemia and pigmentation (co-secretion of other peptides) Ectopic ACTH secretion due to an indolent carcinoid tumour can be indistinguishable from Cushing's disease
Adrenal dependent	Adrenal adenoma Less commonly carcinoma and rarely hyperplasia	Some adrenal adenomas secrete cortisol	Tend to also secrete androgens, presenting with hirsutism and/or virilisation, e.g. clitoromegaly

Normally the enzyme 11β-hydroxysteroid dehydrogenase (11β-OHSD) in renal tubules converts cortisol, which has high affinity for the mineralocorticoid receptor (producing aldosterone activity), to cortisone, which does not. Any endogenous cause of Cushing's syndrome, with excess cortisol, has potential to produce excess aldosterone activity, but with ectopic ACTH diseases, which evolve rapidly, very high amounts of ACTH flood the 11β-OHSD enzyme system and cause build up of cortisol that cannot be converted to cortisone fast enough, so producing Cushing's syndrome with substantial biochemical disturbances of hyperaldosteronism (hypokalaemia) and few morphologically Cushingoid features. Case 2.14, Box 2.41, discusses aldosterone causes of hypertension and Case 2.25, Table 2.56, discusses aldosterone's role in potassium disorders.

Box 5.56 **Initial clues to Cushing's syndrome (in order of frequency)**

- Obesity/weight gain (centripetal distribution)
- Facial plethora
- Round face
- Decreased libido
- Thin skin
- Menstrual disturbance (amenorrhoea and infertility)
- Hypertension
- Hirsutism
- Depression/emotional change
- Easy bruising
- Glucose intolerance
- Weakness (proximal myopathy)
- Osteopenia on X-ray
- Nephrolithiasis

Most discriminating are thin skin, easy bruising and proximal muscle atrophy.

Initial examination

- As for acromegaly, there are lengthy lists of signs to be found in textbooks, some insulting ('buffalo hump' and 'moon face'), which may best be summarised as signs of corticosteroid excess. Recognising these is often not hard (Fig. 5.89).

Further assessment

- Consider iatrogenic Cushing's syndrome. Most patients with Cushing's syndrome are taking long-term corticosteroids for a chronic inflammatory disease such as chronic obstructive pulmonary disease, asthma or inflammatory bowel disease, or a renal transplant. Cushing's syndrome results from prolonged exposure to excessive circulating glucocorticoid, and, except where the diagnosis is iatrogenic, should be confirmed biochemically.
- The three non-iatrogenic or endogenous causes of Cushing's syndrome to consider are shown in Table 5.51. Endogenous Cushing's syndrome is more common in women. Rarely, pseudo-Cushing's syndrome may result from obesity, depression or sometimes alcohol excess.
- Explore concerns.

Feedback to patient

Your symptoms would suggest the possibility of a condition called Cushing's syndrome. This can cause all of the symptoms you have been experiencing and lead to high blood pressure and diabetes, and also ultimately osteoporosis. It is due to excess secretion of a hormone called cortisol. There are numerous causes for this phenomenon. The pituitary gland at the base of the brain produces numerous hormones including a hormone that stimulates excess cortisol secretion. We should arrange blood tests to check the levels of cortisol and related hormones in order to confirm that this is Cushing's syndrome, and then consider a scan of the pituitary area, and potentially other tests, to try to identify the specific cause, as well as seeking the advice of a hormone specialist/endocrinologist. We need to understand a little more about what is happening first of all but if this does turn out to be Cushing's syndrome then various treatments are possible, from tablets and radioactive therapy to surgery. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has been gaining weight, becoming hypertensive with impaired glucose tolerance, and

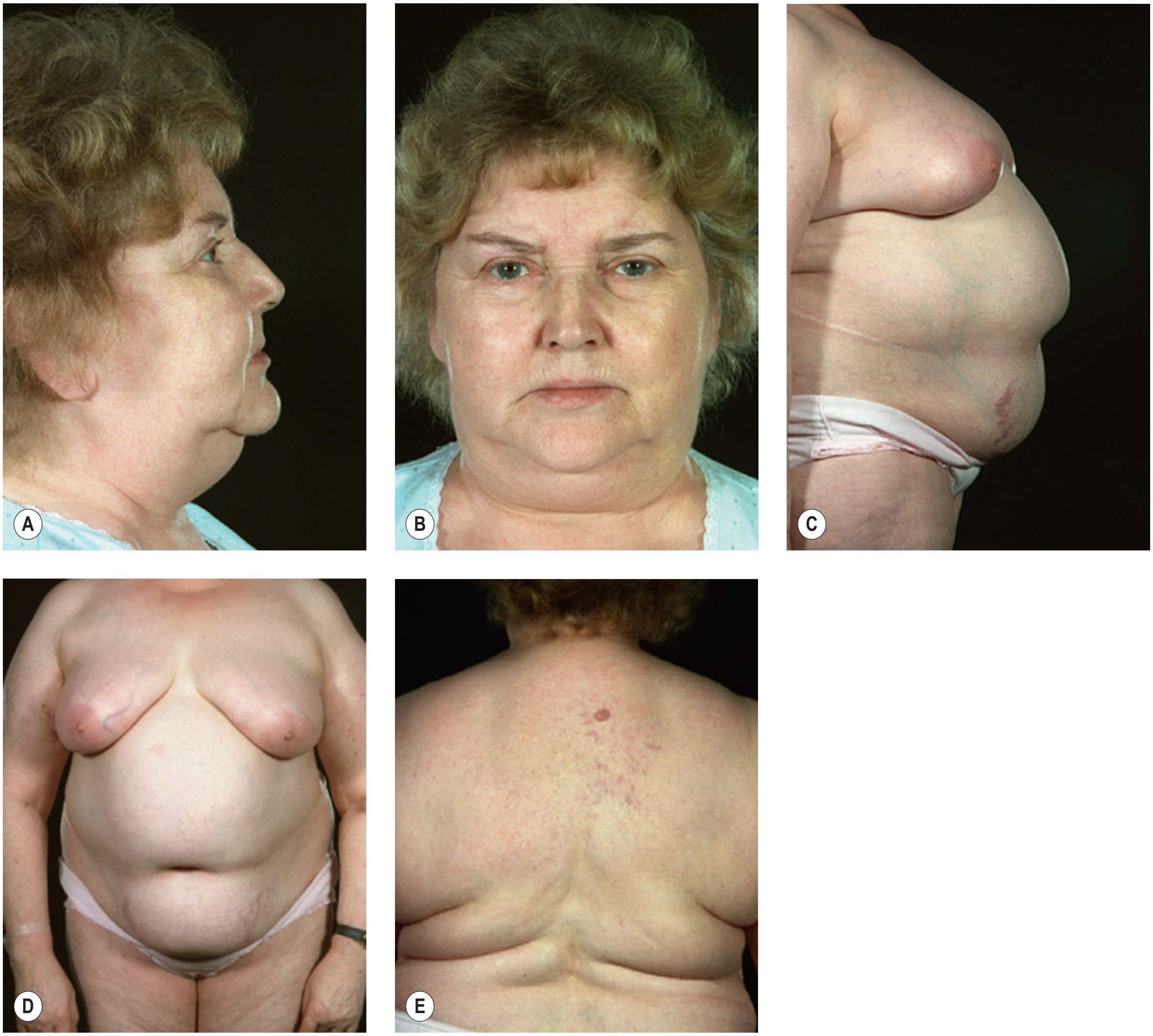


Figure 5.89 (A–E) Cushing's syndrome.

has thin skin, easy bruising and proximal muscle atrophy.

Provide a diagnosis or differential diagnosis with supporting evidence

She does not take steroids and almost certainly has non-iatrogenic Cushing's syndrome – most likely Cushing's disease, although ectopic adrenocorticotrophic hormone and adrenal adenomas also need to be considered.

Outline an investigation and management plan

There are two steps to investigating clinically suspected non-iatrogenic Cushing's syndrome [Table 5.52]:

1. Diagnosing Cushing's syndrome (low-dose dexamethasone suppression test or assessment of circadian rhythmicity or 24-hour urinary free cortisol)
2. Establishing the cause (adrenocorticotrophic hormone detectable – Cushing's disease if partly suppressible so pituitary imaging needed, ectopic adrenocorticotrophic hormone if not suppressible; adrenocorticotrophic hormone not easily detectable – adrenal tumour so adrenal imaging needed)

For Cushing's disease trans-sphenoidal hypophysectomy by an experienced surgeon is the treatment of choice, but potential complications are cerebrospinal fluid rhinorrhoea, diabetes insipidus, hypopituitarism, visual field disturbance, persistent or recurrent disease and death. Laparoscopic bilateral adrenalectomy is

Table 5.52 The two steps to investigating non-iatrogenic Cushing's syndrome

Step	Tests				Interpretation	Diagnosis
1. Diagnosing Cushing's syndrome Three types of test; sometimes repeated tests needed since cyclical secretion of cortisol recognised in some patients	**Low-dose dexamethasone suppression tests** Most commonly used test All causes of Cushing's syndrome fail to suppress Normal subjects and those with pseudo-Cushing's suppress Two types of test		**Overnight dexamethasone suppression test** 1 mg dexamethasone (a synthetic glucocorticoid) administered at 23.00		Cushing's syndrome if plasma cortisol > 50 nmol / l at 08.00–09.00	Cushing's syndrome
			48-hour dexamethasone suppression test More sensitive test 0.5 mg dexamethasone administered 6-hourly at 09.00,15.00, 21.00 and 03.00 for 2 days		Cushing's syndrome if plasma cortisol > 50 nmol / l	Cushing's syndrome
	Assessment of circadian rhythmicity Normal cortisol levels at 08.00–09.00 tend to be in the range 150–650 nmol / l, may be in a range around half that at 16.00, and can drop to a nadir of < 50 nmol / l at midnight Normal circadian rhythmicity lost in Cushing's syndrome		Test requires admission to hospital – Cushing's syndrome excluded if single sleeping plasma cortisol < 50 nmol / l		At 48 hours, single unstressed sleeping midnight plasma cortisol > 50 nmol / l is most sensitive test for Cushing's syndrome but it is generally not practical to admit patients for 48 hours, necessary to allow circadian rhythmicity, prior to the test (late night salivary cortisol an alternative with slightly lower sensitivity)	Cushing's syndrome
	24-hour urinary free cortisol				Positive if ≥ 275 nmol / 24 hours, but low sensitivity (usually tested on up to three occasions)	Cushing's syndrome
2. Establishing the cause	**Plasma adrenocorticotrophic hormone (ACTH; corticotrophin)** – derived from pro-opiomelanocortin, its gene expressed by ACTH tumours	**ACTH easily detectable** (ACTH-dependent cause)	**High-dose dexamethasone suppression test (HDDST) or alternatively corticotrophin releasing hormone (CRH) test**	**ACTH partially suppressible** ↓ **Pituitary imaging**	Pituitary adenomas to an extent obey normal physiological rules with HDDST, albeit with higher threshold for suppression than the normal situation – around 80% of Cushing's disease suppress to < 50% of basal levels, i.e. a low sensitivity test Magnetic resonance imaging now standard but sometimes unsatisfactory since pituitary adenomas can be small and undetectable yet detectable 'incidentalomas' are common Bilateral inferior petrosal sinus sampling with measurement of ACTH following CRH stimulation can diagnose and permit hemispheric localisation of adenoma, and theoretically permit hemispheric resection with preservation of pituitary function	**Cushing's disease**
				ACTH not suppressible ↓ **Imaging for cause**	Ectopic ACTH not suppressible, but exceptions recognised	**Ectopic ACTH**
		ACTH not easily detectable (corticotrophin independent / adrenal-dependent cause)	**Imaging for adrenal tumour**		Adrenal cortisol production suppresses ACTH	**Adrenal tumour**

increasingly used in refractory cases. Lasting remission without other pituitary hormone deficiency is achievable in over 50% of patients. Pituitary radiotherapy is the next best choice, and used if there is persistent hypercortisolism after surgery. The main complication is progressive anterior pituitary failure, which may be subtle and protracted, sometimes not detectable for as much as 10–20 years. Cortisol levels have usually normalised within a few years, and later growth hormone deficiency, gonadotrophin deficiency and hypoadrenalism are not uncommon. Drugs are sometimes used before surgery or after failed surgery, and include metyrapone and ketaconazole, which inhibit cortisol synthesis. Metyrapone causes an increase in androgen precursors and hirsutism. Mitotane is sometimes used in adrenocortical carcinoma. There is interest in agents that might inhibit adrenocorticotrophic hormone release. Unilateral adrenalectomy is the treatment of choice for an isolated adrenal adenoma and bilateral adrenalectomy is reserved for hypercortisolism in Cushing's disease where primary evacuation or treatment is not possible; it may be complicated by Nelson syndrome, in which adrenocorticotrophic hormone levels rise causing melanin-induced hyperpigmentation.

CASE 5.37 HYPOADRENALISM AND ADDISON'S DISEASE

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

> Re: Mr Michael Frogmore, aged 39 years
>
> This man has weight loss and weakness. He has noticed increased skin pigmentation.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 39-year-old man who has been losing weight over recent months and feeling nauseated and very tired. You have also noticed an increase in skin pigmentation on your palms and around your mouth and face. You do not feel dizzy when you stand up. You do not have any past medical history or take any medications. You wonder what is wrong with you, as you are not normally someone who feels under the weather.

Box 5.57 **Symptoms of hypoadrenalism**

- Anorexia and weight loss (> 90%)
- Fatigue
- Weakness
- Postural dizziness
- Nausea, vomiting, diarrhoea
- Reduced libido and axillary hair
- Sweating
- Salt craving

Focused history and examination

Initial history

- Ask about symptoms of hypoadrenalism (Box 5.57), which can be insidious. Hyperpigmentation is the result of elevated melanocyte-stimulating hormone and adrenocorticotrophic hormone and suggests primary adrenal failure, usually Addison's disease.

Initial examination

- Look for *hyperpigmentation*, especially of *skin creases* (*palms*, *elbows*), the *lips* and *mouth*, and *surgical scars* (Fig 5.90). There may be *vitiligo*, and sparse *axillary* (and pubic) *hair*. *Postural hypotension* is possible.

Further assessment

- Consider other causes of hypoadrenalism / adrenal insufficiency (Table 5.53).
- Adrenal crises are associated with haemodynamic instability and life-threatening metabolic disturbances. State that you would measure blood pressure. Hyponatraemia and hyperkalaemia with type IV renal tubular acidosis are common, owing to mineralocorticoid deficiency. Hypoglycaemia is less common but possible. Addison's disease carries a two-fold increased risk of mortality.
- Explore concerns.

Feedback to patient

Your symptoms would suggest the possibility of a condition called Addison's disease. This can cause all of the symptoms you have been experiencing and lead to low blood pressure and alterations in blood chemistry. It is due to deficiency of hormones produced by the adrenal gland, a gland above the kidneys that produces hormones called cortisol and fludrocortisone, which are lacking in Addison's disease. We should arrange blood tests to confirm that this is Addison's disease, as well as tests on blood chemistry. This is a very treatable condition, and we would expect you to feel well again with treatment, but we need to establish the diagnosis

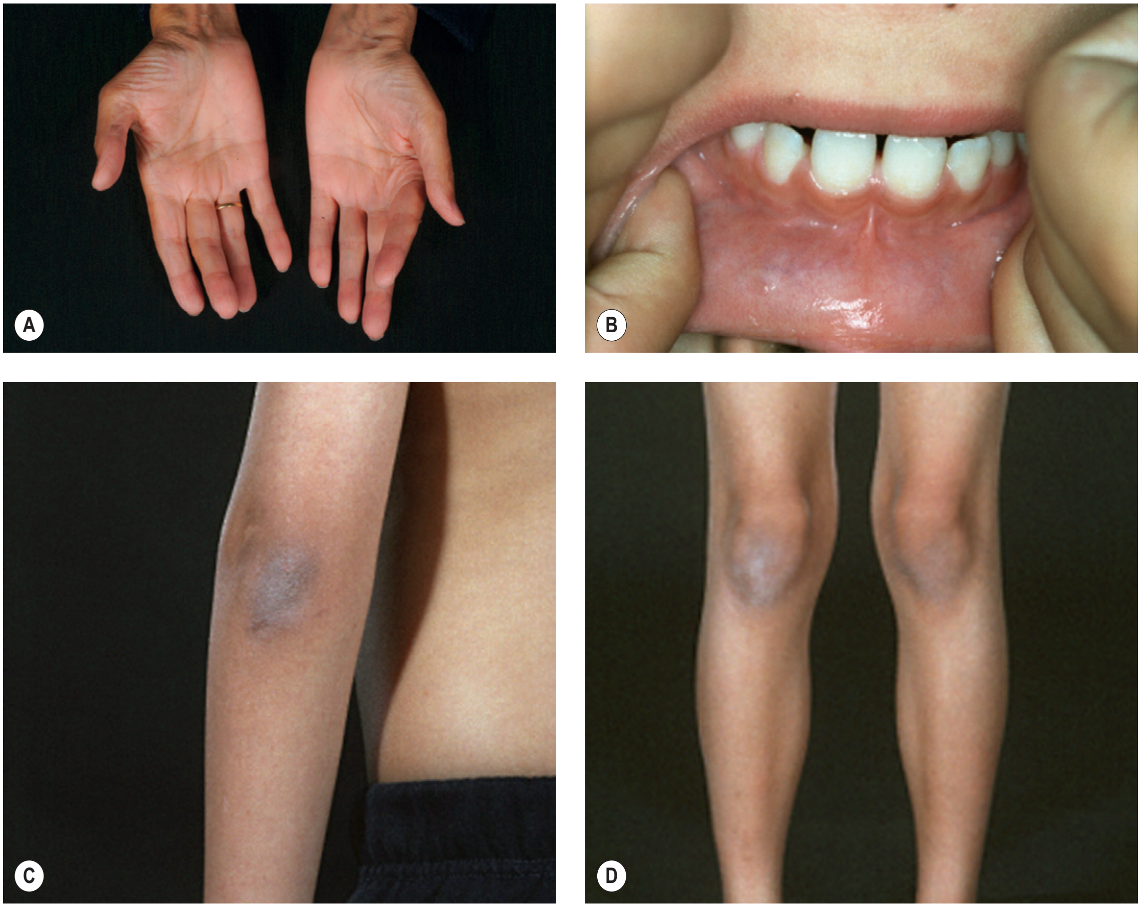


Figure 5.90 Addison's disease: hyperpigmentation of (A) palms, (B) mouth, (C) elbows and (D) knees.

first of all. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has symptoms and signs suggesting Addison's disease, notably the skin pigmentation associated with tiredness, nausea and weight loss.

Provide a diagnosis or differential diagnosis with supporting evidence

Other causes of hypoadrenalism should always be considered, although the pigmentation suggests Addison's disease. Hypopituitarism sometimes seems clinically similar. Addison's disease tends to appear over months or up to 2–3 years with hyperpigmentation, whereas hypopituitarism can take a more protracted course over many more years especially if radiotherapy is a cause, and pallor predominates. An adrenocorticotrophic hormone level usually resolves the issue, although levels of other pituitary hormones might be indicated.

Outline an investigation and management plan

A serum cortisol level ≤ 100 nmol/l at 09.00 h is diagnostic of hypoadrenalism, and elevated adrenocorticotrophic hormone is suggestive. The tetracosactrin or short Synacthen test is used to confirm a suboptimal response to synthetic adrenocorticotrophic hormone: 250 μg is administered intramuscularly and serum cortisol is measured at 0, 30 and 60 minutes. A normal response is a peak of more than 550 nmol/l, although definitions vary. The result may be less easy to interpret, with a suboptimal response, for people who have just stopped or are on low-dose, long-term prednisolone. Switching to dexamethasone is a potential way of assessing in these circumstances.

Adrenal antibodies to adrenal enzymes are present in over 90% of patients with adrenal autoimmunity, although most people with adrenal antibodies without symptoms do not develop adrenal insufficiency. Elevated recumbent renin with low or normal aldosterone may be a sign of impending hypoadrenalism where a cause is not confirmed. Other tests include chest and abdominal imaging.

Adrenal ‘incidentalomas’ are asymptomatic findings on 2–8% of scans. Most are adenomas, and these may be non-functioning or lead to subclinical autonomous glucocorticoid hypersecretion, Conn’s syndrome or phaeochromocytoma. Other incidentalomas are metatases, carcinoma, myelolipoma and many less common types. Biochemical tests to aid diagnosis include the low-dose dexamethasone suppression test for hypercortisolism, renin and aldosterone levels for aldosteronism and plasma or urinary catecholamines or metanephrines for phaeochromocytoma. Computed tomography scan can distinguish between adenomas and non-adenomas based on lipid content.

Table 5.53 Causes of hypoadrenalism

Cause	Features
Autoimmune destruction (Addison’s disease	Hyperpigmentation Addison’s disease usually occurs in isolation, although it is frequently associated with other organ-specific autoimmune diseases associated with HLA DR3 or DR4, e.g. type 1 diabetes, thyroid disease and pernicious anaemia; rarely, it is part of one of the genetically determined autoimmune polyglandular syndromes with various modes of inheritance – type 1 may involve chronic mucocutaneous candidiasis, hypoparathyroidism and Addison’s disease; type 2 always includes Addison’s disease, and may include thyroid disease (Schmidt syndrome) or diabetes
Metastatic disease	Relatively common, e.g. lung, breast, kidney, melanoma, lymphoma Hypoadrenalism less common
Infection	Human immunodeficiency virus associated, e.g. cytomegalovirus Tuberculosis Fungal infection, e.g. histoplasmosis, coccidioidomycosis More common in immunocompromised
Infiltration	Granulomatous disease Haemochromatosis Amyloid
Iatrogenic	Ketoconazole, rifampicin, phenytoin
Critical illness	Hypotension can be both the cause (hypoperfusion / infarction) and effect of hypoadrenalism
Haemorrhage	Waterhouse–Friderichsen syndrome (infarction in meningococcal septicaemia)
Congenital	Adrenoleucodystrophy
Secondary to pituitary disease	

The adrenal cortex secretes the glucocorticoid cortisol, the mineralocorticoid aldosterone, and androgens. Aldosterone secretion is predominantly under the control of renin–angiotensin, but around 10% is controlled by adrenocorticotrophic hormone. Glucocorticoid, mineralocorticoid and androgens are reduced in adrenal failure, albeit not until around 90% of functioning tissue is lost, whereas only glucocorticoid activity is affected by adrenocorticotrophic hormone deficiency.

Treatment of hypoadrenalism involves identification and management of any underlying remediable cause and adrenal replacement therapy with both glucocorticoid and mineralocorticoid. Hydrocortisone is administered at a starting dose of 10 mg on waking (to mimic the physiological peak), 5 mg at lunchtime and 5 mg at 18.00 h. An increased dose may be needed in pregnancy. Fludrocortisone is used to achieve normal sodium homeostasis, as evidenced by normal plasma renin levels. Androgen replacement remains contentious. Increased doses of hydrocortisone are needed in intercurrent illness, generally doubled orally but with high doses intravenously in unstable patients. An adrenal crisis requires immediate intravenous physiological saline, and 100 mg hydrocortisone iv followed by 50 mg qds.

Corticosteroid withdrawal can precipitate iatrogenic hypoadrenalism. If prednisolone has been used for under 3 weeks at doses of < 40 mg, it can usually be withdrawn abruptly. If this is not the case, gradual withdrawal is needed. After a few weeks of treatment it could be decreased in 2.5 mg decrements for a few days to 7.5 mg and then more slowly, e.g. 2.5 mg every week or every few weeks. After an unknown period it could be decreased in 2.5 mg decrements once or twice monthly to 7.5 mg and then more slowly, e.g. 1–2.5 mg monthly. If disease is likely to recur then reduction is often by 1 mg monthly.

CASE 5.38 HIRSUTISM AND POLYCYSTIC OVARIAN SYNDROME

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Michelle Short, aged 34 years

This overweight woman is being treated in hospital for pneumonia, and getting better. She mentions to you that she has noticed weight gain and hirsutism over recent months.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 34-year-old overweight woman recovering in hospital from pneumonia. You mention to the doctor that you have noticed weight gain and hirsutism and male pattern baldness over recent months. You have recently been diagnosed with hypertension and impaired glucose tolerance. You are particularly concerned about the abnormal hair distribution, and about problems with fertility.

Focused history and examination

Initial history

- Ask about symptoms and duration.
- Ask about past medical history and drugs.

Initial examination

- There is *hirsutism*, or excessive hair growth, particularly over the face and limbs (Fig. 5.91). There may be *acne*. There may be other *signs of hyperandrogenism*.

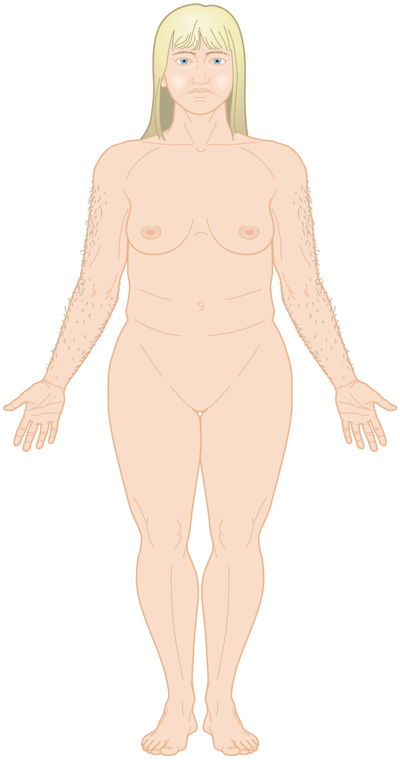


Figure 5.91 Hirsutism.

Hypertrichosis refers to excess body hair. Hirsutism refers to excess hair in androgen-dependent areas (male pattern). Hyperandrogenism or 'virilisation' refers to male pattern hair loss and other physical changes including voice change, breast atrophy and clitoromegaly. Hirsutism may be constitutional, or it may be the result of adrenal or ovarian disorders, such as androgen-secreting tumours in either of these organs. It may be caused by congenital adrenal hyperplasia – a group of autosomal recessive disorders, the commonest defect being 21-hydroxylase deficiency, this enzyme defect resulting in a deficiency of glucocorticoids or mineralocorticoids leading to hyperstimulation of the adrenal gland, which can only respond by producing excess hormones from unaffected pathways – testosterone precursors and testosterone. There can be a spectrum of clinical manifestations from severe ambiguous sexual differentiation at birth and precocious puberty in males, to mild, late-onset signs resembling polycystic ovarian syndrome (PCOS) with virilisation in females. One of the most common causes of hirsutism is PCOS.

Further assessment

- Ask about fertility.
- Ask about hypertension and diabetes.
- Explore concerns.

Feedback to patient

> The hair growth, weight gain, problems with blood pressure and blood sugars, and problems with fertility may all be part of a wider condition called polycystic ovarian syndrome in which insulin, the hormone controlling blood sugar and growth, does not work effectively. Sometimes there are cysts on the ovaries. There are treatments for the various aspects of the condition but it is a highly specialised area with a number of alternative diagnostic possibilities. I would prefer not to jump to conclusions at this stage and for us to consider running some blood tests and possibly an ovarian scan and seeking a more senior and specialist opinion. I can see that there is a range of very important concerns that you have and it is essential that we take things forward and help you. I'd be happy to answer any further questions that I can.

Feedback to examiners

Summarise the key history and examination findings

> This woman has hirsutism, some signs of hyperandrogenism and features of the metabolic syndrome. She is particularly concerned about fertility.

Provide a diagnosis or differential diagnosis with supporting evidence

> She probably has polycystic ovarian syndrome. The possibility of a virilising adrenal tumour causing Cushing's syndrome should always be considered in the differential diagnosis.

Box 5.58 **Polycystic ovarian syndrome (PCOS)**

PCOS is the commonest endocrine disorder in women. The aetiology and pathophysiology remain unclear, but both genetic and environmental factors are involved.

PCOS typically presents with symptoms of anovulation due to hyperplasia of ovarian thecal cells and multiple cysts, associated with clinical and/or biochemical evidence of androgen excess. The spectrum of presentation, however, includes hyperandrogenism with amenorrhoea, oligomenorrhoea or regular periods. As well as being the most common cause of anovulatory infertility or subfertility, PCOS is a major risk factor for development of type 2 diabetes.

Diagnosis is made primarily clinically, but typical biochemical features are raised serum concentrations of testosterone (and androstenedione) and elevation of serum luteinising hormone, particularly in anovulatory women, with a raised luteinising hormone to follicle-stimulating hormone ratio and abnormalities in the usual pulsatile secretion of gonadotrophin-releasing hormones. Oestradiol levels are usually normal or elevated, and mild hyperprolactinaemia may occur. In overweight and obese women an oral glucose tolerance test should be undertaken to detect impaired glucose tolerance reflecting insulin resistance with hyperinsulinaemia, and high-density lipoprotein cholesterol levels are low.

Management of PCOS includes treatment of infertility, menstrual regulation in those who do not desire pregnancy and treatment of associated symptoms of hyperandrogenism. Diet and lifestyle change in overweight and obese women with PCOS is important to improve fertility and prevent or reduce possible long-term consequences of the metabolic disturbances characteristic of anovulatory women with PCOS.

Outline an investigation and management plan

Polycystic ovarian syndrome is characterised by a number of clinical and biochemical abnormalities and there is a range of treatment considerations [Box 5.58].

CASE 5.39 GYNAECOMASTIA AND HYPOGONADISM

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr William Gale, aged 70 years

This man is being treated in hospital for pneumonia, and getting better. He mentions to you that he has noticed breast enlargement recently.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

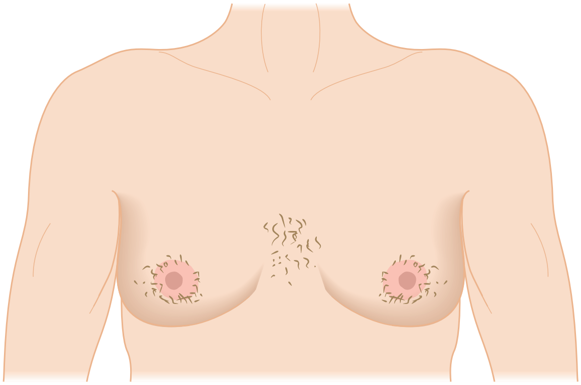


Figure 5.92 Gynaecomastia.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old man recovering in hospital from pneumonia. You mention to the doctor that you have noticed bilateral breast enlargement over the past few months. A year ago you were in hospital with heart failure and since then have been on treatment with ramipril and spironolactone. You are more curious than alarmed, as having excessive breast tissue does not worry you too much at your age.

Focused history and examination

Initial history

- Ask about symptoms and duration.
- Ask about past medical history and drugs.

Initial examination

- There is *gynaecomastia* (Fig. 5.92).

Gynaecomastia may be difficult to distinguish from normal breast tissue but the patient's account of a change should be given credence. Gynaecomastia is caused instead by a decreased androgen–oestrogen ratio and so galactorrhoea (usually due to hyperprolactinaemia) is not expected.

Further assessment

Gynaecomastia has many causes (Box 5.59).

A full hormone, including gonadotrophin, profile would be important, together with assessing for features of testosterone deficiency, in instances where a clear cause is not evident. Testosterone-deficiency symptoms should be assessed where a clear cause is not evident.

Testosterone deficiency is increasingly recognised, and not uncommon. It may result from a specific hypogonadal

Box 5.59 **Causes of gynaecomastia**

- Puberty
- Drugs, e.g. digoxin, spironolactone, cimetidine
- Older age
- Chronic liver disease (oestrogens)
- Klinefelter's syndrome (XXY) – gynaecomastia, small testes, azoospermia, raised gonadotrophins
- Hypopituitarism
- Carcinoma of lung or liver
- Testicular failure
- Thyrotoxicosis

disorder or age-related decline. It may be hypergonadotrophic or hypogonadotrophic. Hypergonadotrophic hypogonadism refers to primary testicular failure, often with elevated follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels. Acquired causes include mumps, trauma, torsion, surgery, radiotherapy, drugs (spironolactone, chemotherapy, marijuana) and myotonic dystrophy. Congenital disorders include Klinefelter's syndrome and 5α-reductase deficiency (androgen resistance). Hypogonadotrophic hypogonadism refers to gonadal failure secondary to hypothalamic/pituitary disease, usually with low or normal FSH and LH levels. Systemic disorders including chronic kidney or liver disease, and sickle cell disease can also cause testosterone deficiency. Chronic alcohol excess is a common cause. Testosterone deficiency can present in many ways, most commonly as reduced libido, reduced muscle mass, reduced bone mass with an increased risk of osteoporosis, reduced facial, body or pubic hair, small testes or non-specific cognitive changes such as poor concentration or tiredness.

- Explore concerns.

Feedback to patient

This looks like a condition called gynaecomastia, which refers to benign enlargement of breast tissue. It can sometimes be produced by drugs like spironolactone and depending upon whether or not you would wish us to try to tackle the problem we could alter your medication. However, it would be sensible to review your cardiac assessment from a year ago before considering any switch in treatment. I'd be happy to answer any further questions or concerns that you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has gynaecomastia. He is unconcerned.

Provide a diagnosis or differential diagnosis with supporting evidence

The cause is likely to be spironolactone, and there are no symptoms of a wider problem.

Outline an investigation and management plan

Further investigation should be necessary only if the gynaecomastia progresses or if new features develop.

CASE 5.40 PSEUDOHYPOPARATHYROIDISM

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Ralph Lloyd, aged 27 years

This young man is recovering from an exacerbation of asthma in hospital and has a lifelong abnormality of his hands.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 27-year-old man with pseudohypoparathyroidism and shortened fourth and fifth fingers of both hands. You have lived with this problem without difficulty and your general practitioner monitors your blood tests. You are currently in hospital with asthma and take the opportunity to ask the doctor about whether or not this condition affects calcium levels, as you have heard there is an association.

Focused history and examination

Initial history

- Ask about the condition and the details known to him.

Initial examination

- There are *short fourth and fifth metacarpals* on both hands. There is short stature, obesity, a round face with frontal bossing of the skull and a short neck (Fig. 5.93).

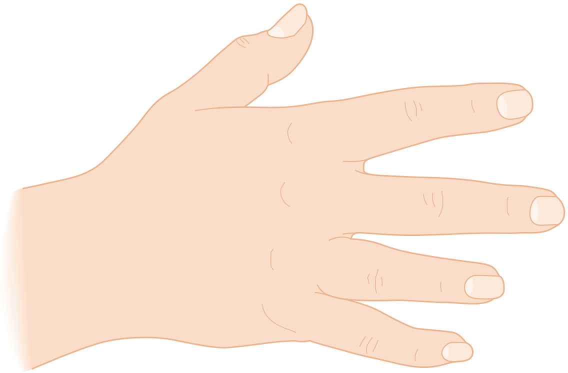


Figure 5.93 Pseudohypoparathyroidism.

Further assessment

Calcification can be a complication of pseudohypoparathyroidism, as might be learning difficulties, hypothyroidism and hypogonadism. Short stature has many causes (Box 5.60).

- Explore concerns.

Box 5.60 **Causes of short stature**

- Familial
- Achondroplasia
- Turner's syndrome (45X0) – short stature, primary amenorrhoea (low oestrogen levels with raised follicle-stimulating hormone and luteinising hormone levels) and delayed puberty; there may be a webbed neck and widely spaced nipples, and sometimes there is a horseshoe kidney or aortic coarctation
- Noonan's syndrome

Feedback to patient

Pseudohypoparathyroidism is a condition in which a hormone in the body, parathyroid hormone, cannot work effectively because of a block to its action. This potentially causes disturbances in the body's calcium levels, which may be low, which is why your general practitioner monitors your blood tests. It is also associated, in some forms, with shortened metacarpal bones on the fourth and fifth fingers.

Feedback to examiners

Summarise the key history and examination findings

This man has short fourth and fifth metacarpals on both hands and short stature.

Provide a diagnosis or differential diagnosis with supporting evidence

The syndrome with short fourth and fifth metacarpals is likely to be the result of type 1a pseudohypoparathyroidism or pseudopseudohypoparathyroidism.

Hypoparathyroidism is a biochemical condition comprising low levels of parathyroid hormone and calcium and raised phosphate.

Pseudohypoparathyroidism is the result of target organ resistance to parathyroid hormone, with high levels of parathyroid hormone, low calcium and raised phosphate (type 1a or Albright's hereditary osteodystrophy produces this phenotype although there is also a morphologically normal phenotype).

Pseudopseudohypoparathyroidism has the morphological appearance of type 1a pseudohypoparathyroidism with normal biochemistry.

Outline an investigation and management plan

This is a specialist area but after diagnosis is made simple surveillance may be all that is required.

Other problems in acute and general medicine and elderly care

Cases

CASE 5.41 CHEST PAIN POST-MYOCARDIAL INFARCTION

Candidate information

Role

You are a doctor on the cardiac ward.

Scenario

Re: Mr Thomas Carter, aged 84 years

This man has chest pain after a recent heart attack.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are an 84-year-old man admitted to hospital 3 days ago with a small heart attack. You have a long history of ischaemic heart disease and heart attacks and your cardiologist has performed angiograms in the past that have shown considerable disease and you and he have jointly agreed to manage things with tablets and not to consider coronary artery bypass grafting, and coronary stenting is not feasible. You are quite pragmatic, and have pain not infrequently, and prefer to continue with the 'conservative' treatment strategy. Indeed your main concern is that the doctors will want to do more. You currently take aspirin 75 mg, clopidogrel 75 mg, optimum statin therapy, optimum beta blockade therapy and optimum angiotensin blockade therapy. Your subcutaneous heparin was stopped yesterday. Your pain is not as severe as that which brought you into hospital but of the same character and came on at rest.

Focused history and examination

Initial history

- Establish that the pain is likely to be cardiac.
- Get a sense of how things have changed symptomatically.

Initial examination

- Examine for signs of heart failure.
- Xanthelasmata (Fig. 5.94) are more common in people with coronary disease, reflecting dyslipidaemia, but are not present in most people with coronary disease.

Further assessment

- Consideration of other causes of chest pain is always wise (pulmonary embolus if pleuritic, pericarditis if positional) but coronary disease is the likely cause.
- Explore concerns.
- Respect his thoughts, but make sure that his decision for symptomatic treatment only is based on informed knowledge. Chest pain after recent myocardial infarction suggests ongoing coronary instability (chest pain after recent coronary intervention suggests possible restenosis, warranting urgent re-evaluation of coronary anatomy).

Feedback to patient

I suspect you are having further angina or just possibly another heart attack. We should repeat your ECG. We'll give you some oxygen and a nitrate spray just now, and restart the heparin injections. Some morphine might help, too, if the pain isn't settling quickly. Then I'd hope to keep things settled with some additional treatment (e.g. nitrate orally, nicorandil). I'll also arrange for you to have a blood test in a few hours to see if a further small heart attack has occurred. We can also let your cardiologist know that you have had further pain. I'd be happy to try to answer any questions you may have.

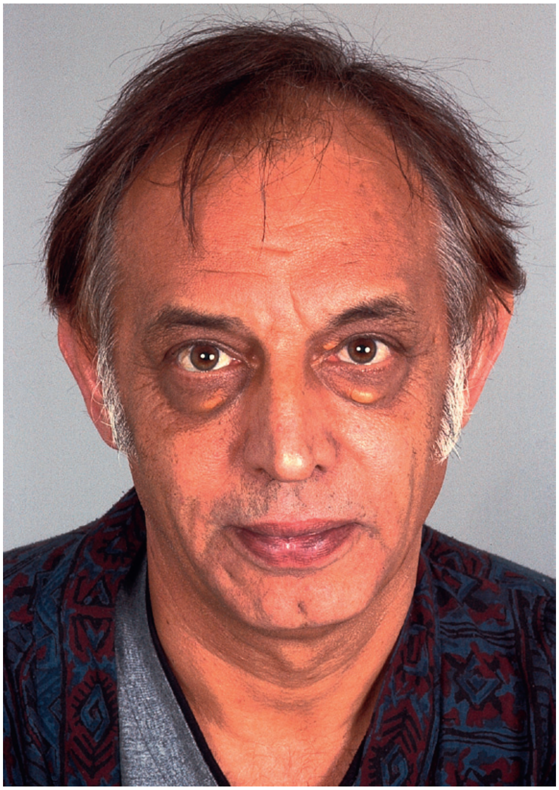


Figure 5.94 Xanthelasmata.

Feedback to examiners

Summarise the key history and examination findings

This man has typical cardiac ischaemic pain at rest post-myocardial infarction.

Provide a diagnosis or differential diagnosis with supporting evidence

The diagnosis on history alone is probably post-coronary syndrome unstable angina or a further myocardial infarction.

Outline an investigation and management plan

His decision for non-escalation of investigation, particularly invasive investigation, is probably based on previous information and discussion with his cardiologist. This should be respected, although it is always important to ensure that decisions are made with appropriate information.

CASE 5.42 SUDDEN BREATHLESSNESS

Candidate information

Role

You are a doctor on the medical ward.

Scenario

> Re: Mrs June Havelock, aged 70 years
>
> This woman is recovering from pneumonia in hospital and has become more breathless.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 70-year-old woman in hospital with pneumonia. You have been recovering well over the past few days, but have been kept in hospital because of your unstable diabetes and because you developed a problem with your platelet count when being given heparin injections for prevention of blood clots. Today you have suddenly started to feel more breathless. You are usually well apart from the diabetes and only take medication for this. You wonder what might be wrong, are a little worried about worsening pneumonia and wonder what should be done as you have had antibiotics already.

Focused history and examination

Initial history

- Ask about the onset (abrupt or gradual).
- Ask about other symptoms (e.g. cough, sputum).
- Ask about pleuritic pain.
- Ask about past medical history and drug history.
- Ask about a personal or family history of blood clots.

Initial examination

- Note whether she is tachypnoeic. Examine her chest, notably through auscultation.
- You would wish to know her observation recordings including saturations.

Further assessment

Explore concerns.

Feedback to patient

We need to find out why you are feeling more breathless. My chief concern is that you might have developed a blood clot on the lung. I think we should arrange a chest X-ray and then a scan of the lungs to see if there is evidence of further infection or if a blood clot on the lung might be a possibility. It is particularly important for us to answer this question without delay because of the problems you have had with the heparin injections. On that basis I will talk with the radiologists now about the X-ray and scan, and also speak with our haematology expert about a safe alternative to heparin. I'd be happy to try to answer any other questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman is suddenly more breathless after a period of medical illness and could not take heparin.

Provide a diagnosis or differential diagnosis with supporting evidence

Pulmonary embolus must be considered more likely than recurrence or exacerbation of infection. Heparin-induced thrombocytopenia is much more commonly complicated by thromboembolic complications than bleeding.

Outline an investigation and management plan

A computed tomography pulmonary angiogram is necessary, and immediate discussion with a haematologist about an alternative to heparin.

CASE 5.43 UPPER GASTROINTESTINAL BLEEDING

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Mr Malcolm Freeman, aged 35 years
>
> This man has had an episode of haematemesis and melaena.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the

Box 5.61 **Managing gastrointestinal bleeding**

Non-variceal upper gastrointestinal bleeding

- Arterial haemorrhage, a non-bleeding visible vessel or adherent blood clot should be considered for endoscopic treatment (injection in combination with either heat application or clips, i.e. two therapies are important).
- A high-dose intravenous proton pump inhibitor should be given immediately after endoscopic therapy to patients at high risk of rebleeding, but not for other patients and not prior to endoscopy (insufficient evidence).
- A second-look endoscopy should be considered within 24 hours with re-treatment of any residual high-risk lesions.
- Bleeding uncontrolled by endoscopy should be managed with repeat endoscopic therapy, selective arterial embolisation, or surgery.
- Anti-platelet and non-steroidal anti-inflammatory drugs should be discontinued where possible.
- *Helicobacter pylori* should be sought and eradicated.

Variceal bleeding

- Risk assessment includes calculation of the Rockall score. For patients with a high likelihood of varices, terlipressin 2 mg intravenously then 4–6 hourly for 72 hours (contraindicated in ischaemic heart disease) or therapeutic doses of another vasopressin analogue, continued for several days after endoscopic confirmation and treatment, is indicated.
- Broad-spectrum antibiotics are indicated prior to endoscopy (e.g. cefotaxime and metronidazole).
- Oesophageal varices diagnosed at endoscopy are best treated by variceal band ligation, gastric varices by cyanoacrylate injection.
- After initial haemostasis, repeat endoscopies with further band ligation are indicated, with a non-selective beta blocker until all varices are obliterated.
- Balloon tamponade is potentially dangerous (significant risks of aspiration pneumonia and oesophageal rupture). It should be used as rescue therapy only in actively bleeding patients when haemorrhage continues despite endoscopic therapy; it may stop bleeding temporarily until definitive endoscopic, radiological, or surgical treatments are applied.
- Transjugular intrahepatic portosystemic stent shunting (TIPSS) should be considered for uncontrolled variceal bleeding.
- TIPSS should be considered to prevent oesophageal rebleeding in patients with contraindications to endoscopic or pharmacological treatment, and in patients who bleed despite endoscopic and drug treatments.

Lower gastrointestinal bleeding

- After resuscitation, the site and cause may be determined by endoscopy or computed tomography (CT). CT angiography or digital subtraction angiography are preferred in massive active bleeding.
- Colonoscopic haemostasis is an effective means of controlling haemorrhage from active diverticular or post-polypectomy bleeding.
- For bleeding uncontrolled by colonoscopy, arterial embolisation may be indicated.
- When bleeding fails to respond to endoscopy or interventional radiological procedures, localised segmental intestinal resection or subtotal colectomy may be indicated.

remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 35-year-old solicitor. Over the past few days you have been vomiting. Initially you thought it had been provoked by a meal, but the vomiting persisted and in the past 24 hours you have been vomiting with a mixture of blood. You have no other symptoms but you felt light-headed and your general practitioner noted your blood pressure to be low and arranged urgent admission to hospital, where you have just arrived. You have recently taken over-the-counter non-steroidal anti-inflammatory drugs for stomach pains. You cannot accept a blood transfusion on religious grounds.

Focused history and examination

Initial history

- Ask about dyspepsia, haematemesis and melaena.
- Ask about symptoms of postural hypotension.
- Recognise that gastrointestinal bleeding and presyncopal symptoms warrant urgent assessment.

Initial examination

- Look at the observations, especially heart rate, lying and standing blood pressure and respiratory rate.

A normal or low heart rate and hypotension may occur in acute haemorrhage, often after gastrointestinal surgery – the first response to maintain arterial pressure despite a falling cardiac output involves tachycardia and baroreceptor reflex vasoconstriction; a second phase, however, occurs when about a third of circulating volume has been lost, in which sympathetically mediated vasoconstriction and cardiac drive fall abruptly and cardiac vagal drive increases.

Further assessment

- Consider the causes of upper gastrointestinal bleeding (Case 2.3).
- Haematemesis (bright red, dark clots or coffee-ground) or melaena indicate an upper gastrointestinal bleed. Haematemesis suggests a source of bleeding proximal to the ligament of Trietze (jejunum). Small bowel (e.g. angiodysplasia, investigated by wireless capsule endoscopy or computed tomography angiography) and right-sided colonic disease may present with melaena. The

Rockall score (see Case 2.3) is a clinical and endoscopic predictor of risk of re-bleeding and death. The Blatchford score (Case 2.3) is a risk score that does not rely on endoscopy; its place is more to predict the need for intervention than to predict mortality, and so it has greater emphasis in less severe bleeding.
- Explore concerns.

Feedback to patient

You are almost certainly bleeding internally, probably from the stomach, possibly from an ulcer. This could be due to one of a number of things, or a combination, including the anti-inflammatories. In the first instance we need to put a 'drip' into you, take a blood sample and give you some fluid intravenously and some medication to help settle things. There is a small possibility, if your blood count is very low, that you would need a blood transfusion to stabilise things. I appreciate that you would not wish to accept this on religious grounds and we would respect this (assuming capacity). We should, when things are more stable, with or without a blood transfusion, arrange an endoscopy test – a camera test looking into the stomach. You should be aware that if there is bleeding that cannot be controlled or if the blood count is unsafely low, then not having a transfusion could be a decision that would put you at serious risk. I'd be happy to try to answer any further questions.

Feedback to examiners

Summarise the key history and examination findings

This man has had an upper gastrointestinal bleed.

Provide a diagnosis or differential diagnosis with supporting evidence

Possible causes are peptic ulceration, oesophagitis, erosive disease, varices or a Mallory–Weiss tear.

Outline an investigation and management plan

He needs stabilisation and then oesophagogastroduodenoscopy. [Management strategies for upper and lower gastrointestinal bleeding are described in Box 5.61 (and further discussed in Cases 2.3 and 2.6, respectively).]

CASE 5.44 NON-BLANCHING RASH

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mrs Amanda Baker, aged 34 years

This woman is in hospital recovering from pyelonephritis. She has developed bruising on her legs.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 34-year-old woman, usually well, recovering from a kidney infection. You have been on antibiotics. You have developed a bruising type of rash on your legs. It is not painful and you feel well. It has progressed over the past 2 days. You have finished your course of antibiotics. You wonder what might be wrong with the legs, and are worried about leukaemia as a friend died of this last year presenting with bruising initially.

Focused history and examination

Initial history

- Ask about symptoms such as pain.
- Ask about the onset and duration of the rash, and if she has ever had a similar rash before.
- Ask whether she feels generally well despite it.
- Ask about past medical history and drug history. Ask particularly about any known bleeding tendency.

Initial examination

- Ask whether it is painful or tender (erythema nodosum).
- Note a *non-blanching, purpuric rash*. This is skin vasculitis, and the purpura *may be palpable* (Fig. 5.95).

Further assessment

The clinical appearance of vasculitis is usually obvious, but the type may need to be confirmed by biopsy.

- Consider causes of skin vasculitis (Box 5.62).
- Explore concerns.

Feedback to patient

I think this may be something called a leucocytoclastic vasculitis, a condition well recognised after infections and antibiotics, and one which invariably settles down. However, we should check your temperature, arrange some blood tests and obtain a chest X-ray, and I'd also like to ask a dermatologist – a skin specialist – to have a look at the rash. If it is not settling it may be that he or she would wish to take to a biopsy (a small piece of tissue) from the rash and consider some treatment to settle it down more quickly. I'd be happy to try to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has a non-blanching rash of her legs and feet that has progressed over days rather than hours and she feels well without other symptoms.

Provide a diagnosis or differential diagnosis with supporting evidence

She probably has a localised skin vasculitis secondary to the infection or the antibiotics. Less likely possibilities include erythema nodosum from the same triggers (but she does not have the typical tender bruising pattern) or a clotting disorder. The skin vasculitis is probably a leukocytoclastic vasculitis but other possibilities include immunoglobulin A vasculitis and urticarial vasculitis. Immunoglobulin A vasculitis is an immunoglobulin A-mediated vasculitis causing a linear immunofluorescent pattern histologically. It is seen in immunoglobulin A disease such as Henoch–Schönlein purpura. Urticarial vasculitis looks like urticaria but lasts for over 24 hours, turns to bruises, and is painful rather than itchy. It is seen in autoimmune disease such as lupus.

Outline an investigation and management plan

I would check urinalysis, renal function and obtain a chest X-ray. Autoimmune testing for systemic vasculitis is usually negative in patients with isolated skin vasculitis who feel well. Leukocytoclastic vasculitis is a cutaneous vasculitis that may occur in isolation or in association with systemic disease including anti-neutrophil cytoplasmic antibody-associated vasculitis, connective tissue disease, infection (e.g. infective endocarditis, hepatitis B virus, hepatitis C virus), inflammatory bowel disease or paraproteinaemia. Consideration of causes is important but the rash usually settles.

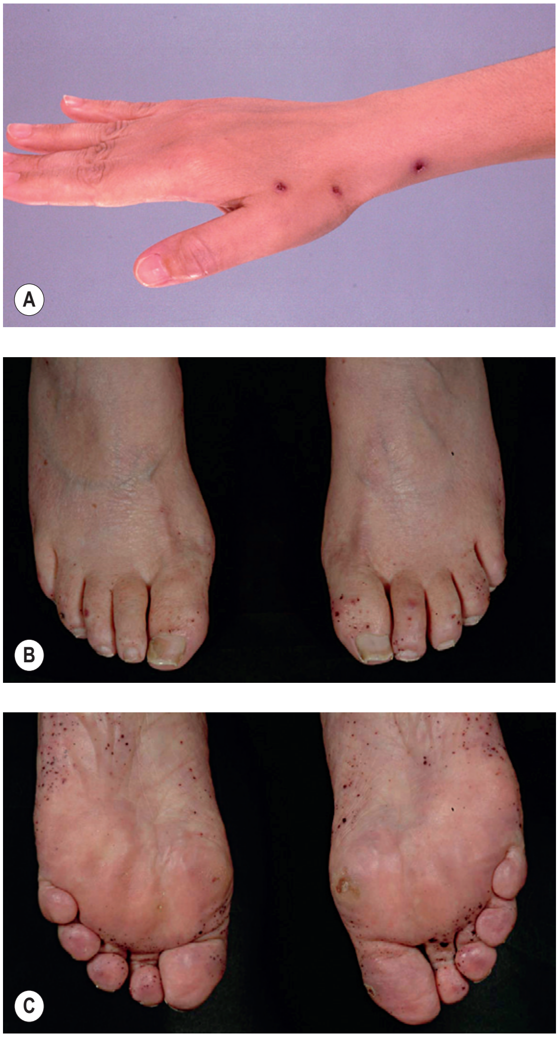


Figure 5.95 Vasculitis: (A) hand, (B) dorsum, (C) soles of the feet.

Box 5.62 **Causes of skin vasculitis**

- Primary systemic vasculitis (Case 2.28)
- Autoimmune connective tissue disease, e.g. rheumatoid arthritis, systemic lupus erythematosus, scleroderma
- Drug reactions
- Infective endocarditis
- Henoch–Schönlein syndrome
- Prothrombotic disease, e.g. antiphospholipid syndrome
- Cryoglobulinaemia
- Lymphoproliferative disease

CASE 5.45 SKIN AND SOFT-TISSUE INFECTION AND ACUTE DERMATOLOGY

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

> Re: Ms Julia Summers, aged 39 years
>
> This woman has a painful red leg.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 39-year-old woman with type 1 diabetes. You have developed a spreading, red, tender calf and thigh over the past few days. You have developed a small area of skin breakdown that is very uncomfortable, but the skin is now very tender even where intact. Ten days ago you were bitten by a 'mozzie'. You wonder what might be wrong with the leg, are worried about infection and wonder what should be done. You are a nurse.

Focused history and examination

Initial history

- Ask about the leg and how painful it is.
- Establish whether there are any systemic or febrile symptoms.
- Ask about the stability of the diabetes.

Initial examination

- There is *erythema* over the anterior aspect of the lower leg, which is *warm*, and slightly swollen (Figs 5.96 and 5.97).

The main differential diagnosis of unilateral leg swelling is deep venous thrombosis (DVT), which causes circumferential swelling of the leg, often with erythema or discoloration with calf predominance and calf tenderness; Wells' criteria for diagnosing DVT are discussed in Case 2.36. Bilateral erythema in the setting of lower limb oedema, although commonly treated as soft-tissue infection, is more often a problem with venous stasis, as bilateral swollen legs seldom imply infection.

Further assessment

- Cellulitis is usually caused by staphylococcal or streptococcal infection. The term erysipelas is often used to describe deeper, often streptococcal, infection with greater demarcation of erythema. In practice it may be hard to distinguish the type of soft-tissue infection. However you should always also consider necrotising fasciitis (Fig. 5.98). Pain and tenderness are disproportionately predominant and visible signs may be minimal, especially early on. Necrotising fasciitis refers to infection that spreads rapidly through fascial layers, often extending through a limb within hours. Erythema is minimal and not always present. Bullae or vesicles are common, but late, signs. Black, necrotic skin is also a later sign, and often more obvious than erythema. Although traditionally streptococcal organisms are responsible, many cases of necrotising fasciitis are of mixed growth, and some cases may be caused by less rapidly progressive organisms (relatively) such as streptococcal group G organisms. Both creatine kinase and C-reactive protein serum levels may be raised, but are unreliable in excluding necrotising fasciitis if normal.
- Explore concerns.

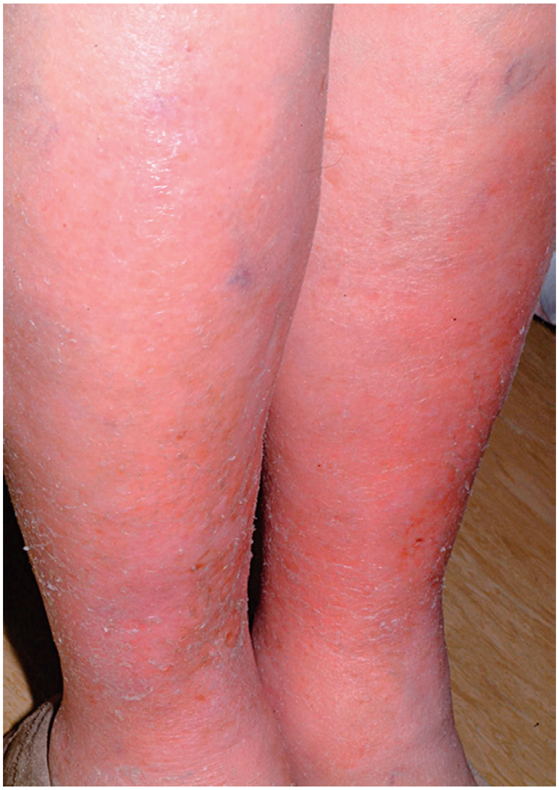


Figure 5.96 Cellulitis.

Feedback to patient

I think this is cellulitis. It is certainly a very nasty case. We should take a series of blood tests and start you on intravenous antibiotics. If things are not settling soon we may also need to consider a scan of the leg, and we should certainly have you on a prophylactic dose of subcutaneous heparin. Given the degree of tenderness and the ulcer, I'd also like to just play on the safe side and ask our microbiology team and our surgical team to have a

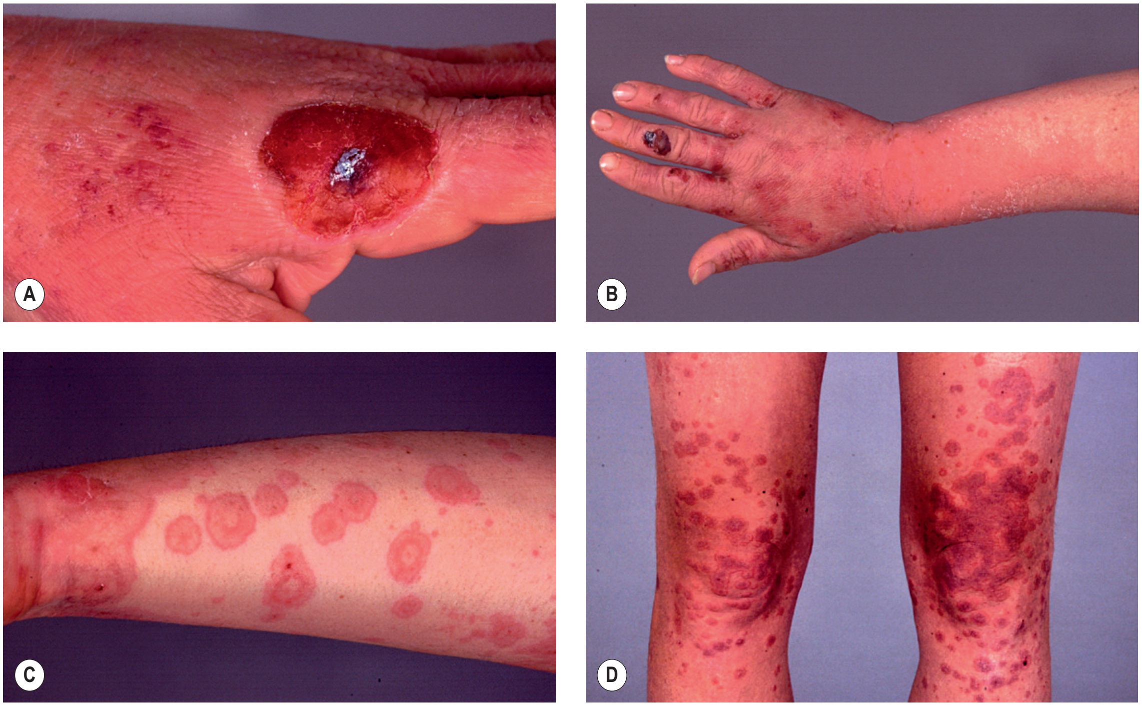


Figure 5.97 (A–D) Erythema multiforme due to orf with secondary soft-tissue infection.

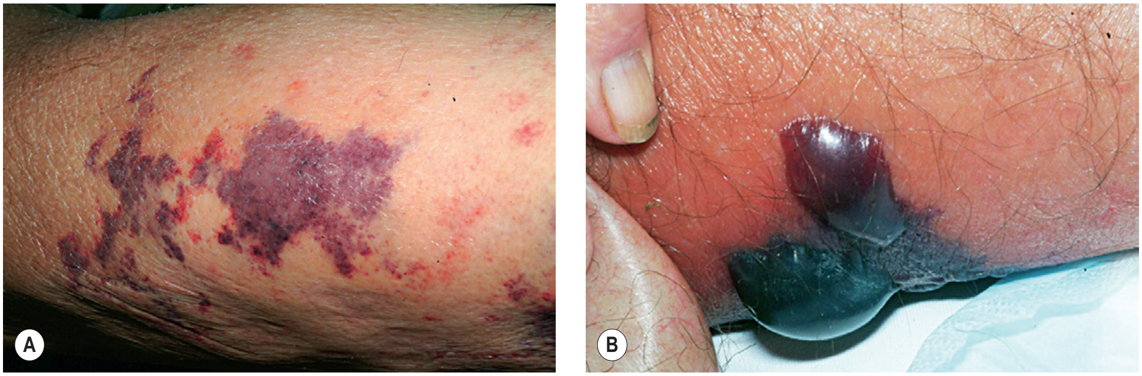


Figure 5.98 (A, B) Necrotising fasciitis.

look at the leg. Occasionally infection can run through the deeper layers of tissue leading to more serious problems if not tackled early. I don't think this is the case but I would prefer to treat this situation aggressively than watch and wait. I'd be happy to try to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has diabetes with spreading erythema on her leg following an inset bite 10 days ago. There is a small area of ulceration [Box 5.63] that looks infective.

Provide a diagnosis or differential diagnosis with supporting evidence

She probably has cellulitis, with circumferential redness. A deep vein thrombosis is possible but this looks much more like cellulitis, although if there is any doubt about symptoms and signs settling quickly with antibiotics an ultrasound scan of the leg will be indicated. However the degree of tenderness makes me just a little edgy about the possibility of necrotising fasciitis – an emergency [Table 5.54].

Box 5.63 **Ulcers**

Types of ulcer

An ulcer is a breach in the skin and may be caused by trauma, infection or vasculitis, and perhaps most commonly in older people with pressure, venous insufficiency, arterial compromise, oedema or lymphoedema.

Pressure ulcer

This is a breach in the skin and underlying tissue secondary to unrelieved pressure, shear or friction. Pressure may be high for a short time or low for a longer time, as in sacral pressure ulcers caused by immobility in a chair or bed. Friction pressure ulcers commonly occur at the heels, elbows and knees, and may be associated with poor manual handling or positioning, and are common in agitated patients. Shearing, when gravity overcomes friction as when a patient slides down the bed, commonly causes pressure ulcers on the buttocks, sacrum or back. Other factors conspire to increase pressure ulcer risk or worsen pressure ulcers such as poor nutrition, body weight, incontinence and comorbidity such as cardiovascular disease. The European Pressure Ulcer Advisory Panel classification system describes four grades of pressure ulcer:

- *Grade 1*: Non-blanchable erythema of intact skin; discoloration, warmth, oedema, induration or hardness
- *Grade 2*: Partial-thickness skin loss involving epidermis, dermis or both; superficial, appearing as abrasion or blister
- *Grade 3*: Full-thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, fascia
- *Grade 4*: Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full-thickness skin loss.

Treatments

Treatments for ulcers depend upon the cause, e.g.:

- *Pressure*: Pressure-relieving devices, modern dressings, e.g. hydrocolloids, hydrogels, foams, films, alginates, silicones; antimicrobials
- *Venous*: Appropriate compression bandages, especially in prevention (light, moderate, high or extra-high compression)
- *Arterial*: Surgery; vasodilators, e.g. pentoxylline, iloprost
- *Vasculitic*: Treatment of underlying cause, immune suppression
- *Ulcer with lymphoedema*: Compression bandages; intermittent pneumatic compression device
- *Exuding cavity*: Vacuum-assisted closure
- *Ulcer with slough and non-viable tiss*ue: Debridement, e.g. sharp, mechanical, enzymatic, biosurgery (maggots)
- *Necrobiosis lipoidica*: Psoralen and ultraviolet light therapy.

Table 5.54 Acute dermatology

Infection	Cellulitis Erysipelas Impetigo (blistering superficial staphylococcal infection) Infected blisters, e.g. insect bites Necrotising fasciitis Tinea Scabies
Psoriasis	Erythrodermic / generalised pustular Guttate
Atopic dermatitis	Secondary infection Eczema herpeticum
Autoimmune bullous diseases	Pemphigoid / pemphigus
Urticaria	This refers to wheals (oedema) surrounded by flares of erythema. It may be caused by drugs, heat, cold, pressure, water, food substances, infections, insect bites or dermatographism. More severe reactions may lead to angioedema. Urticaria pigmentosa refers to itchy red-brown macules / papules, which are the dermal manifestation of systemic mastocytosis.
Angioedema	Food allergens, e.g. peanuts Drug reactions, e.g. ACE inhibitors, mediated by bradykinin C1 esterase inhibitor deficiency
Photosensitivity	Sunburn Polymorphic light eruption – more urticarial than sunburn, common in young females, semi-confluent Drug-induced phototoxicity
Exanthems and similar eruptions	Acute viral and streptococcal Herpes simplex / varicella-zoster Erythema multiforme Measles

Table 5.54 Acute dermatology—cont'd

Vasculitis	Cutaneous vasculitis and Henoch–Schönlein purpura Meningococcal infection
Tumours	Cutaneous metastases Paraneoplastic eruptions
Drug eruptions	An inexhaustible list of drugs can be the cause of a skin eruption, e.g. ACE inhibitors, allopurinol, antibiotics, antiepileptic drugs, NSAIDs, thiazides. Morphologically, the eruption may be: • Morbilliform (exanthematous, maculopapular) – extensive and variably itchy, onset a few days after drug, usually lasts under a week, responds to moderate potency topical steroid • Urticarial or angioedematous – treatment with antihistamines, epinephrine (adrenaline) and possibly systemic steroids • Eczematous • Psoriasisiform • Lichen planus-like • Bullous • Pustular • Acne-like • Vasculitic • Pityriasis rosea-like • Photosensitive
	Life-threatening drug eruptions are: • TEN due to, for example, antibiotics, terbinafine, nevirapine, NSAIDs, antiepileptic drugs (lamotrigine, valproate low risk), allopurinol, gold or sulfasalazine. • Stevens–Johnson syndrome, a cousin of TEN but also provoked by infections, e.g. herpes simplex virus • Drug reaction with eosinophilia and systemic symptoms (DRESS), a rare, multisystem disease with rash, fever, lymphadenopathy, pneumonitis, hepatitis, eosinophilia and atypical lymphocytosis
Erythroderma	
Erythroderma is a clinical syndrome with extensive red skin and systemic manifestations which may be life threatening. If 70–90% of the skin is red it is termed 'sub-erythroderma'. There are many causes, e.g. eczema, psoriasis, drugs, cutaneous T-cell lymphoma, staphylococcal scalded-skin syndrome, pityriasis rubra pilaris.	
Severe skin shedding	
Bacterial scalded skin syndrome is the most quoted cause, but TEN due to drugs (any) or autoimmunity is another important cause. Glucagonomas can cause a necrolytic migrating erythema.	
Itch	
Primary skin diseases causing itch include all types of dermatitis, lichen planus, blistering disorders, especially dermatitis herpetiformis (pemphigoid does not itch), fungal infection or mite infestation, flea / tick bites and ichthyosis (dry skin with fish-like scales, with a genetic basis or associated with malignancy). Systemic causes include drugs, cholestasis, uraemia, diabetes, hyper / hypothyroidism, polycythaemia vera, lymphoma, parasitophobia and certain drugs. Dermographism, in which itchy linear lines appear after scratching, is common, as are heat- and cold-induced urticaria, the former often after a hot shower or bath, or after exercise. Aquagenic itch caused by water of any temperature is recognised, as is neurogenic itch in which neuropathic pain is rather manifested as itch.	

ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; TEN, toxic epidermal necrolysis.

Outline an investigation and management plan

She should receive intravenous antibiotics guided by the microbiology team. If necrotising fasciitis is considered a possibility, urgent surgical review with a view to urgent fasciotomy is needed to establish the diagnosis, and extensive surgery is the only potential cure, aided by appropriate antimicrobials.

CASE 5.46 SWOLLEN LEG

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Mrs Abigail Booker, aged 38 years

This woman complains of pain in her left calf and she feels it may be swollen.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 38-year-old woman who thought your left calf was a little swollen and tight feeling over the past 2 days and today it is quite painful when you walk. You went on holiday to Egypt 3 weeks ago and you returned home 1 week ago. Your left calf had been slightly uncomfortable the whole time you were away. You thought it was probably due to the heat although you were surprised that only one leg was affected. Now, since coming home, the problem has got worse. You tend to have mild discomfort in the left knee from a cartilage injury when you played tennis some years ago. You do not feel breathless nor do you have any chest pain. You have no other symptoms or problems. Your only treatment is the oral contraceptive pill. You are now on the acute medical unit and wonder what might be wrong with the leg, are a little worried about a clot and wonder what should be done.

Focused history and examination

Initial history

- Ask about the leg symptoms.
- Ask about risk factors (flight, oral contraceptive pill, any family history).
- Ask about possible pulmonary embolus symptoms (chest pain, breathlessness).

Initial examination

- Examine the calves.

Further assessment

- If deep vein thrombosis seems likely, seek any possible contraindications to anticoagulation.

Feedback to patient

I think there is a reasonable possibility that you do have a blood clot in the leg, known as a deep vein thrombosis. The flight may have been a risk factor for this. The oral contraceptive pill does modestly increase the risk although usually not enough to provoke a blood clot on its own. Some people do have an increased tendency to clot, which is why I asked about any family history. We need to arrange for you to have a scan of the leg to confirm our suspicions but in the mean time it is important to start some blood-thinning medication (an injection of heparin) pending the result. I'd be happy to try to answer any other questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has a swollen calf without convincing signs of cellulitis.

Provide a diagnosis or differential diagnosis with supporting evidence

She has risk factors for a deep vein thrombosis and this must be the first diagnosis to exclude.

Outline an investigation and management plan

A Doppler ultrasound scan of the leg veins is necessary with low-molecular-weight heparin at treatment dose administered pending the result.

CASE 5.47 FOCAL NEUROLOGICAL SYMPTOMS – AMAUROSIS FUGAX

Candidate information

Role

You are a doctor on the medical ward.

Scenario

Re: Mr Alexander Miller, aged 59 years

This man, who is an ex-smoker and has stable type 2 diabetes and peripheral vascular disease, has had an episode of transient loss of vision whilst on your ward recovering from cellulitis.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 59-year-old man in hospital with a foot infection. You also have atrial fibrillation and diabetes. You have just had an episode of sudden painless loss of vision, like a curtain coming across your left eye. It lasted for around 15 minutes and slowly the vision came back to normal. You take aspirin, a statin and metformin. You are an ex-smoker. You are worried about the implications for driving as you live in an isolated area.

Focused history and examination

Initial history

Pick out some key words or points from the information you have been told. The vision loss must be explored. You are told that the diabetes is stable and that he is recovering from cellulitis and a focused history would not tend to explore these areas although you would note the diabetes and smoking (a focused history would not be troubled with how many he smoked) as risk factors, along with the atrial fibrillation.

- Confirm sudden, painless, unilateral and transient visual loss.
- Ask if it is a first episode.
- Exclude any symptoms of retinal tearing or posterior vitreous detachment (flashes or floaters).
- Exclude any other focal neurological symptoms (limb weakness or sensory loss, speech disturbance).

Initial examination

- Confirm that there are no other obvious focal neurological features, and auscultate the carotid arteries for bruits and possibly the heart briefly.
- Note blood pressure.
- Perform a quick bedside visual acuity and fundoscopy.

Further assessment

- Explore his concerns about driving.

Feedback to patient

This sounds very much like a transient ischaemic attack or TIA ('mini-stroke'). It is usually caused by a blood clot going into the retina of the eye. The clot then dissolves and the symptoms improve. Clots usually arise from the carotid artery in the neck or from the heart, and the irregular rhythm in the heart may be a source of blood clots, or the previous smoking, which can lead to furring up of arteries in the neck. We should organise a scan of the neck (carotid duplex) and a brain scan, and I would be keen to discuss things further with the stroke team. If the neck scan showed a significant blockage in the relevant artery then a procedure to unblock that blockage may need to be considered by a specialist in vascular surgery. And it may be that following the tests we should consider a more powerful treatment to thin the blood such as warfarin; in the meantime we should increase the dose of aspirin that you take. If, as we suspect, this has been a TIA then you would be required to not drive for a month providing you remain well [it does not matter if you do not know the driving restrictions after a TIA – do not hazard a guess! – and simply tell him that there is likely to be a restriction for a limited time and that you will find out what that is]. I'd be happy to try to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has had transient spontaneously reversible monocular visual disturbance, and has a history of atrial fibrillation.

Provide a diagnosis or differential diagnosis with supporting evidence

The diagnosis is almost certainly amaurosis fugax and is unlikely to be anything else with this constellation of symptoms. Transient visual loss for a few minutes is usually ischaemic. If very brief (seconds), or if bilateral, it is often a reflection of perfusion, common in presyncope. He is at risk of further transient ischaemic attacks or strokes, particularly in the next few weeks.

Outline an investigation and management plan

He should have a carotid duplex scan (urgently) and possibly a brain and heart scan, and I would be keen to discuss things further with the stroke team. If the carotid scan showed significant stenosis in the relevant artery then he should be discussed with the vascular team for consideration of endarterectomy. Following tests he should be considered for warfarin rather than aspirin and in the meantime his antiplatelet therapy should be enhanced (aspirin 300 mg plus dipyridamole, although there is increasing evidence for clopidogrel monotherapy), with consideration to intensifying his lipid-lowering therapy and adding antihypertensive therapy to reach target levels. He is advised not to drive for a month after a transient ischaemic attack.

CASE 5.48 TRANSIENT LOSS OF CONSCIOUSNESS

Candidate information

Role

You are a doctor in the medical outpatient clinic.

Scenario

Re: Mr James Hill, aged 84 years

This man is in your clinic and reports an episode of loss of consciousness.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are an 84-year-old man in the medical outpatient clinic. Last week you had an episode of loss of consciousness without warning. You have had numerous episodes of feeling light-headed. You take three antihypertensives for blood pressure. Your wife does not drive.

Focused history and examination

Initial history

- Ask about the circumstances of the loss of consciousness and any prodromal symptoms.
- Ask if it was witnessed.
- Ask about duration (brief with rapid recovery suggests syncope, prolonged suggests a seizure).
- Ask if any injury was sustained.
- Ask how he felt on recovery (back to normal quickly suggests syncope, post-ictal period suggests seizure).
- Review medications.

Initial examination

- Check blood pressure and auscultate the precordium.

Further assessment

Loss of consciousness is usually either syncope (Case 2.41) or a seizure (Case 2.42) or sometimes metabolic (usually hypoglycaemia). Most loss of consciousness is due to syncope, and both syncope and seizure become more common with age. Syncope is usually due to one of three main groups of causes: cardiac syncope, either electrical (e.g. sinus pauses) or structural (e.g. aortic stenosis); orthostatic hypotension, due to either drugs (e.g. antihypertensives) or disease (e.g. diabetes autonomic neuropathy); reflex syncope, either vasovagal syncope or carotid sinus syncope. Cardiac syncope is often without warning. Orthostatic hypotension is often suggested by the drug or disease history. Reflex vasovagal syncope has a typical prodrome and carotid sinus syncope is often suggested by rubbing or movement of the neck such as shaving or reaching up.

- Enquire into these areas.
- Explore concerns.

Feedback to patient

It sounds as though you had a blackout. This could be due to one of a number of reasons – sometimes a problem with the heart's rhythm or one of its valves, sometimes a drop in blood pressure from medications, and sometimes a fainting attack for other reasons. I think that we should look into this in a bit more detail and in the first instance I would like to arrange for you to have an ECG heart tracing and some blood tests. We should check your blood pressure lying and standing up to see if there is a significant drop when you stand. I would then like to arrange for you to have a heart recording over 24 hours to monitor the heart's rhythm (you can wear a small device) and a heart scan. We can take things from there but I'm afraid that whilst we are waiting for answers the DVLA rules are that you should not drive. I'd be happy to discuss any of this in more detail and answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This man has had an episode of syncope.

Provide a diagnosis or differential diagnosis with supporting evidence

The possible causes are cardiac syncope (electrical or structural), orthostatic hypotension (drugs or disease) or reflex (neurocardiogenic) syncope (vasovagal or carotid sinus syncope).

Outline an investigation and management plan

Unless the cause is clearly orthostatic hypotension, and certainly if his ECG is abnormal, he should proceed to ambulatory ECG monitoring and echocardiography. Further tests will depend upon results and ongoing symptoms but could include more prolonged ECG monitoring, tilt testing and carotid sinus massage. He should not drive whilst the diagnosis is uncertain. Thought should also be given to falls risk and bone protection.

CASE 5.49 VERTIGO AND HEARING LOSS

Candidate information

Role

You are a doctor on the acute medical unit.

Scenario

Re: Mrs Deborah Kent, aged 68 years

This woman has been admitted to hospital with disabling vertigo.

Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are a 68-year-old woman who developed a sudden severe sense of the world moving whilst getting out of bed this morning. This has waxed and waned throughout the day but is very debilitating. The symptom is worsened by any movement. You have no other symptoms, and notably no headache, hearing loss or other neurological symptoms. You feel nauseated but have not vomited. You are usually well. You do not know what is wrong and are rather alarmed.

Focused history and examination

Initial history

- Confirm that the symptom is vertigo (Box 5.64).
- Ask about acute hearing loss, other neurological features (e.g. diplopia, facial numbness or weakness, dysphagia, dysphonia, ataxia, limb weakness) and headache.

Initial examination

- The first step is to decide whether a peripheral or central cause of vertigo is likely. A central cause is suggested by hearing loss (Box 5.65), other

Box 5.64 **Vertigo**

Vertigo is the illusion of movement (e.g. the world spinning as if just getting off a playground roundabout) caused by disorders of the labyrinth or its central connections. The vestibular organ detects head motion, so abnormal activity in the vestibular nerves may be interpreted by the brain as self-motion. Nausea and vomiting often accompany vertigo since there are connections between the vestibular nuclei and brainstem centres mediating nausea and vomiting.

Box 5.65 **Sensorineural hearing loss (SNHL)**

Sensorineural hearing loss is popularly attributable to an acoustic neuroma in the cerebellopontine angle. These are overall rarer than perceived as a cause of SNHL and often slowly progressive. Other central causes, which may present abruptly, include demyelination and stroke, each described, but unusual causes of isolated SNHL. The commonest form of SNHL occurs insidiously with age. Sometimes, SNHL is 'idiopathic' (ISNHL) and abrupt, postulated as viral, autoimmune or ischaemic and prompting a standard battery of haematobiochemistry, inflammatory markers, autoimmune screening and a syphlilis test. Magnetic resonance imaging is mandatory. ISNHL is usually unilateral, occasionally bilateral if autoimmune, and has a variable prognosis. Adjacent cranial nerves are not affected. Treatment is with high-dose steroids and, where available, hyperbaric oxygen; aciclovir is recommended if herpes simplex or zoster are even remote possibilities.

As well as hearing loss, unilateral ISNHL produces problems with localisation of sound as stereosound is lost, a problem that the brain may slowly adjust to.

SNHL is vital to distinguish from conductive hearing loss such as wax in the external ear or fluid in the middle ear, conductive hearing loss being much more amenable to treatment. Abrupt SNHL is an emergency.

The audiogram in SNHL

An audiogram has two axes, the *x*-axis on the top representing increasing frequency from 0 and 250 Hz (very low rumbles) on the left to 8000 Hz, the point at which humans start to stop hearing but beyond which dogs can still detect even higher frequencies or pitches, on the right. Little useful hearing in adults occurs beyond 6000 Hz and in age-related SNHL it is these higher frequencies that are impaired first of all. On the *y*-axis downwards is the intensity of sound, in decibels (dB), a logarithmic scale going from 0 at the top to around 100 at the bottom.

An audiologist in a silent room will produce sound at various frequencies and decibels to determine the minimum threshold in decibels that a sound is heard at a particular frequency. Gradually an average map is built up for each ear. As a very general rule, normal hearing detects most frequencies at around 0 dB but it is common to see the threshold a bit higher, at say 5–10 dB, with a tendency for even higher thresholds at higher frequencies; in very good hearing even negative results such as –5 or –10 dB may be seen, especially at lower frequencies and in children.

With SNHL the trend is for a downward sloping line on the graph rather than a horizontal one. The descent may be very early and very steep in severe ISNHL.

As a general rule, sounds heard below 30 dB give rise to adequate hearing, sounds audible at 50–60 dB may be corrected to around 30 dB with a hearing aid, and sounds detected only below 50–60 dB are usually not amenable to treatment without significant sound distortion when sound is amplified.

The audiogram illustrates the amazing spectrum of frequency and loudness detected by the ear, even individual spoken words comprising a vast array of internal differences; hearing words is a function not just of the spectrum of capability of the hearing mechanism but also of an individual's learned interpretation of how these diverse sounds come together to form words.

Vertigo and SNHL

Vertigo, in a sense, represents a 'screaming', diseased nerve that settles when the nerve is more severely damaged and the brain adjusts. It is more likely continuous than paroxysmal when present. Longer term 'swimminess' may occur if only one vestibular apparatus is working, especially when tired.

Tinnitus

Tinnitus is often ascribed to Ménière's disease but in fact is a common feature of any severe SNHL or damage to the vestibulocochlear nerve. It may be a high-pitched whine or hiss or a washing machine whir. It can be alarmingly disabling, a fact often underappreciated since many benign noises in the ear such as awareness of the pulse are often inadvertently reported as tinnitus. Tinnitus may be due to the brain detecting background noise previously blotted out by normal hearing from ear structures; other theories suggest it is due to the hearing compartment in the brain still being receptive whilst its sensory nerve has dwindled, analogous to the sensory experiences of a phantom limb. Rehabilitation training can overcome tinnitus, just as ticking clocks can become inaudible with time, and hearing aid technologies can help.

Box 5.66 **Tests to differentiate peripheral from central vertigo**

The Dix–Hallpike manoeuvre

The Dix–Hallpike manoeuvre is shown in Fig. 5.99.

The head impulse test

The Dix–Hallpike manoeuvre together with the 'head impulse' or 'head thrust' test may be used to rule out central vertigo and rule in benign paroxysmal positional vertigo or acute vestibular neuritis. Head movement towards a labyrinth (or vestibular nerve) causes activation of that labyrinth and reflex movement of the eyes in the opposite direction away from the canal – the vestibular ocular reflex (VOR) – as the eyes attempt to maintain object fixation. The function of the VOR is to stabilise the eyes during fast head movements. The VOR maintains gaze stability by generating eye movements of the same speed as head movements but in the opposite direction. When VOR function is lost, patients see the world jumping around whenever they move their head. With unilateral labyrinth damage and VOR loss the compensatory eye movements and visual fixation fail during sudden movement, and so the eyes continue to move with the head in the direction of the turning of the head towards the damaged labyrinth; this failure is followed by a re-fixating catch-up saccade away from the damaged labyrinth. This can be demonstrated by making a rapid movement of the patient's head in the direction of the damaged labyrinth (or vestibular nerve) – the 'head impulse' or 'head thrust' test (Fig. 5.100). When the head impulse test is positive, the lesion is peripheral and ipsilateral to the direction of head movement (although major brainstem pathology is likely to produce an abnormal VOR). This is reassuring if there are no other symptoms or signs. Bilateral refixation movements are seen frequently in ototoxicity. The head impulse test is normal in central causes of vertigo.

neurological features or headache. Rubbing fingers close to the ears is a crude test of hearing (a formal audiogram is a necessary test if hearing loss is a possibility). Vertigo is not usually an isolated symptom in central causes as the brainstem is a tightly packed grid of long tract and cranial nerve fibres running up and down and across like busy New York City, making it unlikely for an insult to affect only the vestibular nerve or nucleus in isolation. If a peripheral cause is likely, the likely diagnoses are benign paroxysmal positional vertigo or acute vestibular neuronitis. Tell the examiners that you would perform a Dix–Hallpike test and a head impulse test (Box 5.66).

Further assessment

- Further refine the cause of vertigo. Differentiating features are given in Table 5.55.
- Explore concerns.

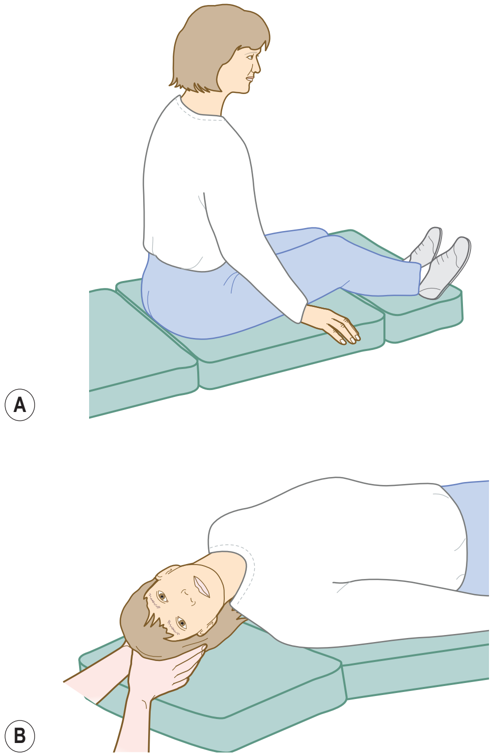


Figure 5.99 Dix–Hallpike test.

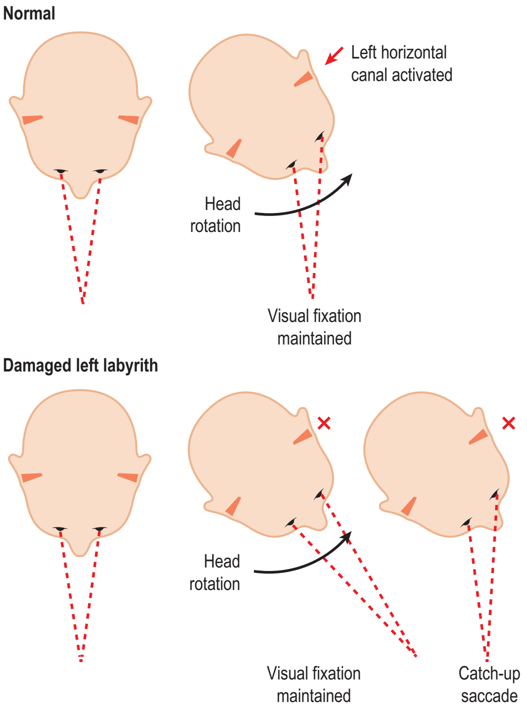

Normal
Left horizontal canal activated
Head rotation
Visual fixation maintained
Damaged left labyrith
Head rotation
Visual fixation maintained
Catch-up saccade

Figure 5.100 Head impulse test.

Table 5.55 Causes of vertigo and differentiating features

Type	Disease	Cause	Vertigo description	Other features	Natural history
Peripheral (three classic causes + rare causes, e.g. suppurative ear disease, vestibular perilymph fistula); some causes may respond to cinnarazine	Benign paroxysmal positional vertigo (common)	Common in later life (but may occur any age) Likely to be due to debris in inner canals	See Box 5.67	Nausea common but vomiting unusual No hearing loss or tinnitus Rotational nystagmus	Responds to Epley manoeuvre if Dix–Hallpike test positive
	Acute vestibular neuritis ('labyrinthitis' or acute vestibulopathy)	Uncertain Viral prodrome in 50%	Symptoms may persist for days or weeks	Nausea and vomiting Hearing loss unusual	Usually resolves within days with vestibular compensation, which precedes nerve regeneration Milder symptoms may recur but over subsequent weeks
	Ménière's disease	Uncommon and cause unknown	Vertigo at any time Chronic and insidious	Tinnitus Hearing loss	Tends to persist
Central	Disease of vestibular connections in brainstem (vertigo is never due to isolated cerebellar disease and causes should not be lumped with those of nystagmus)	• Vertebrobasilar ischaemia (e.g. cerebellopontine or lateral medullary infarction) • Demyelination (may mimic peripheral vertigo) • Space-occupying lesion of cerebellopontine angle (e.g. acoustic neuroma) • Bilateral vestibular failure (otoxicity, e.g. aminoglycoside) • Migrainous vertigo – not widely recognised outside neuro-otological practice; spontaneous or positional vertigo lasting hours to days; typical patient a migraineur with recent increase in headache frequency and vestibular episodes, the headache and vertigo not necessarily occurring together; other migrainous features such as photophobia, phonophobia and nausea often present; many patients have features (including nystagmus) suggestive of central dysfunction so imaging may be required at first presentation; treatment with standard antimigraine agents	Vertigo immediate, persists and does not recover unless underlying cause can be treated May occur in all directions	Red flags pointing to central rather than peripheral vertigo may include: • Acute deafness (the blood supply to the peripheral audiovestibular apparatus can be occluded in some brainstem strokes, the audiovestibular apparatus being supplied by a branch of the anterior inferior cerebellar artery in 90% of people) • Other neurological features (e.g. diplopia, facial numbness or weakness, dysphagia, dysphonia, ataxia, limb weakness) • Headache • Vertical nystagmus	

Feedback to patient

You have vertigo, a condition that is usually caused by a problem affecting the nerve for balance inside the ear. Occasionally it is caused by a problem in the brain itself, but on the basis of your symptoms I think a problem arising in the ear is much more likely. It may well be due to a condition with a complicated name – benign paroxysmal positional vertigo – in which small crystals within the fluid in the ear are affecting its nerve signals and balance. This is easily diagnosed and often easily remedied by a series of head movements we could perform now. I'd be happy to try to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has vertigo. She has no features suggesting a central cause (acute deafness, other neurological features, headache) and thus there is likely to be a peripheral cause.

Provide a diagnosis or differential diagnosis with supporting evidence

The symptoms of positional vertigo, first noticed on getting out of bed this morning, suggest a diagnosis of benign paroxysmal positional vertigo [Box 5.67].

Box 5.67 **Benign paroxysmal positional vertigo (BPPV)**

'Dizziness' is a common symptom, usually caused by presyncope, vertigo or disequilibrium. Balance is a complex mechanism with vestibular, visual and proprioceptive sensory inputs feeding into the brain itself, and with age neuronal reserve is often depleted. Factors that can predispose to balance problems also include depression, ischaemic heart disease, poly-pharmacy, diabetes, postural hypotension and any abnormal gait.

Vestibular input to balance

Vestibular anatomy includes a utricle of semicircular canals (SCCs) positioned in three reciprocal pairs, and in the planes of the extraocular muscles. These are lined with hair cells and filled with endolymph fluid and each has a widened portion called the ampulla. The SCCs act as angular accelerometers, allowing the vestibulo-ocular reflex (VOR) to keep the eyes stable when the head moves. Nerve signals from the hair cells sensing endolymph movement lead into audiovestibular nerve fibres and into the brain, along with information from the cochlear subserving hearing.

BPPV

An abnormal VOR gives rise to the sign of nystagmus and the symptom of vertigo. BPPV is probably the most common cause of vertigo. It is a complex disorder, with subclassification based on the affected SCC. The posterior SCC is affected in most cases.

Classic symptoms

BPPV is characterised by vertigo with nystagmus (character and direction depending upon the part of the inner ear affected) elicited by provocative positions. Classic BPPV is usually triggered by sudden movement from the erect to supine position while angling the head 45° towards the side of the affected ear. Being in the provocative position is not enough – the head must actually move to it. After reaching the provocative position, a latency period of 1–40 seconds occurs before symptoms. When BPPV is triggered, patients feel thrown into a rolling spin toward the side of the affected ear. Symptoms start abruptly and dissipate within 10–60 seconds. This sensation is triggered again upon sitting erect but the direction of the nystagmus is reversed. The first onset is typically sudden. Many patients wake up with it. Symptoms are paroxysmal and positional, most patients experiencing them when rolling over in bed, or reaching upwards or putting their head back as at the dentist. Symptoms and signs fatigue with repeat testing. Attacks may continue for days to weeks, and occasionally months or years. Between attacks, there may be few or no symptoms but in extreme cases the slightest head movement may cause symptoms.

Pathophysiology

Each inner ear contains three SCCs, which mediate spatial orientation, oriented in three perpendicular planes. Each canal consists of a tubular arm (crura) sprouting from a large barrel-like compartment, like the handle sprouting from a mug. Each arm has a dilated (ampullary) end near the top that houses the nerve receptors or crista ampullaris. The crista ampullaris has a sail-like tower, the cupula, that detects fluid (endolymph) flow within the SCC. If a person turns to the right, fluid within the right horizontal canal lags behind, causing the cupula to be deflected left towards the ampulla, translated into a nerve signal indicating the head is turning right. Simply, the cupula acts as a three-way switch, in the neutral position reflecting no motion, and in either direction producing a sensation of movement.

Particles (usually calcium carbonate crystals) in the canal can slow and even reverse movement of the cupula switch, creating signals incongruous with head movements. This mismatch results in vertigo. Two theories in BPPV explain what happens:

1. Cupulolithiasis (cupula stones) refers to densities adhered to the cupula of the crista ampullaris that are not free floating. The situation is analogous to a heavy object on a pole, the extra weight making the pole or cupula unstable and prone to clunking from side to side producing vertigo and nystagmus when tilted backward, especially when the posterior SCC is affected.
2. Canalithiasis (canal stones), proposed by Epley, refers to particles that are free floating and mobile in the posterior SCC. When the head is upright, the particles sit in the canal at the most gravity-dependent position but when tilted supine the particles rotate up along the arc before (after a momentary lag) gravity pulls them down again. This is analogous to pebbles inside a tyre, picked up momentarily when the tyre is rolled before tumbling down again with gravity. This tumbling of particles triggers fluid flow away from the ampulla causing

Box 5.67 **Benign paroxysmal positional vertigo—cont'd**

cupula deflection and nerve-ending stimulation. This produces vertigo and nystagmus. Sitting back up causes reversal of cupular deflection with vertigo and nystagmus beating in the opposite direction. The canalithiasis theory better explains the latency, transient nystagmus and reversal on return to upright that is seen in classic BPPV. Canalithiasis is probably the cause of most cases of BPPV.

Much of this is theory. Perhaps the simplest way to think about BPPV is that hair cells rest in SCCs like sea anemones on the seabed. The anemone tentacles move softly in a watery breeze and the direction they move tells you the direction of that breeze. The brain is able to determine precise body position by integrating information from many anemones in many different planes. If some little crabs or shells or pebbles get into the tentacles of an anemone then it will disrupt tentacle movement and send confusing signals to the brain.

Causes

A few factors predispose patients to BPPV, including inactivity, trauma, ear disease (e.g. Ménière's disease, otosclerosis, sudden sensorineural hearing loss) and central disease. But age is a key factor, with increased otolith cell turnover. Both hair cells and audiovestibular nerve fibres degenerate with age.

Diagnosis

The Dix–Hallpike test (Fig. 5.99) is best performed relatively quickly and with the patient's eyes focused on the nose of the examiner. This provides the best chance of crystal movement. A positive right Dix–Hallpike test is when the patient turns to the right and upbeating, right torsional (rotatory) nystagmus is noted in association with symptoms. By upbeating, right torsional nystagmus we mean that the top part of the iris is seen to flicker up and to the right. It is sometimes called geotropic nystagmus, which means that (in the position the patient is in) the movement is towards the ground. The nystagmus is sometimes referred to as clockwise or anticlockwise, but this is confusing. The opposite (downbeating, left torsional nystagmus) is seen when the patient sits up again. The converse applies for a positive left Dix–Hallpike test.

Classic BPPV involves the posterior SCC and is characterised by:

- Geotropic rotatory nystagmus with the problem ear down – the top pole of the eyes rotates with the fast phase toward the undermost (affected) ear
- Latency (a few seconds)
- Limited duration (< 20 seconds)
- Reversal upon return to upright position
- Response decline upon repetitive provocation.

Purely horizontal nystagmus indicates horizontal canal involvement. Sustained or non-fatiguing nystagmus may indicate cupulolithiasis. Because the type of BPPV is defined by the type of nystagmus, defining it is important.

Treatment

A canalith repositioning procedure (CRP) is favoured treatment. Two major manoeuvres are Epley and Semont, with many minor variations of each. Both involve movements of the head to disperse particles. Semont involves rapid, vigorous, side-to-side head and body movements, and carries concern about complications of vertebral dissection or cervical damage. The Epley manoeuvre is gentler. Research into multiaxial positioning devices that can perform CRP in the proper plane of the SCCs is ongoing.

The Epley manoeuvre (Fig. 5.101) is as follows:

A. Start from the neutral position.

B. The patient is reclined slowly to the supine position of the affected side. The rate is titrated to the point of no nystagmus and no symptoms. This usually takes approximately 30 seconds. The patient is reclined further to the Dix–Hallpike position (15° Trendelenburg, head turned 45° towards the affected side). This usually takes 10 seconds. Another 20 seconds are spent in the Dix–Hallpike position with the affected ear down. Epley's first two steps are thus the same as a Dix–Hallpike test.

C. The patient's head is turned slowly from position B towards the opposite, unaffected side; this moves crystals a little.

D. The body is rolled towards that unaffected side so that the shoulders are aligned perpendicularly to the floor, and the affected ear is uppermost. The head looks 45° below the plane of the horizon to the floor; this moves crystals a lot.

E. The patient is raised back to the sitting position with the head still turned away from the affected side looking over the shoulder. Finally, the head is turned back to the midline.

A Dix–Hallpike test is performed immediately afterwards. If nystagmus is observed, the Epley manoeuvre may be repeated. Then, the patient is instructed to avoid lying completely flat and to avoid agitation of the head for around 48 hours while the particles settle.

Watchful waiting of BPPV may be reasonable if symptoms are infrequent and relatively non-troublesome. Vestibulosuppressant medication is seldom effective. Vestibular rehabilitation can have success after lengthy periods and may include Cawthorne exercises. Surgery is occasionally undertaken in those for whom CRP fails.

Outline an investigation and management plan

Neuroimaging is indicated in vertigo if any of the following are present:

- Acute deafness
- Other neurological features
- Headache
- Intact head impulse test.

Benign paroxysmal positional vertigo is diagnosed by the Dix–Hallpike test [Box 5.66, Fig. 5.99], which reproduces symptoms and induces rotational nystagmus. It can be treated with the Epley manoeuvre [Box 5.67, Fig. 5.101].

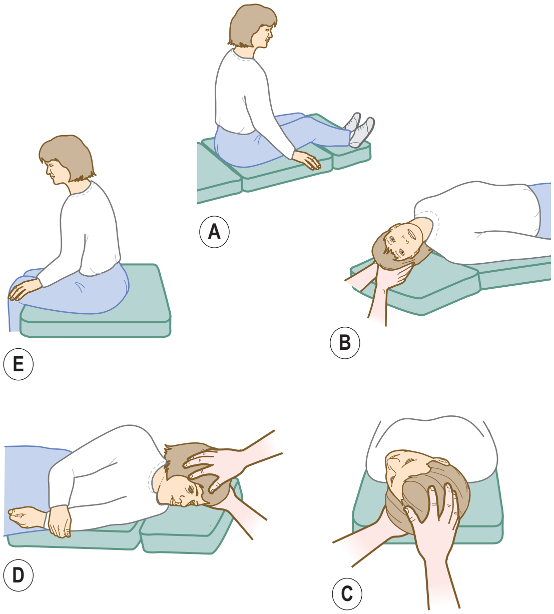


Figure 5.101 Epley manoeuvre.

CASE 5.50 'OFF LEGS' AND 'COLLAPSE'

Candidate information

Role

You are a doctor on an elderly care ward.

Scenario

> Re: Mrs Elizabeth Hunter, aged 89 years
>
> This woman has had numerous falls causing her to be admitted to hospital. On this occasion her daughter is with her following a fall at home in which she did not lose consciousness. Many of the falls have been attributed to urinary tract infections.
>
> Your task is to assess the problem by means of a focused history and focused examination. You should then advise the patient of your probable diagnosis and plan, and address any questions or concerns raised by the patient.

You have 10 minutes. The examiners will alert you when 6 minutes have elapsed, stop you at 8 minutes, and in the remaining 2 minutes ask you to report your findings, the diagnosis or differential diagnosis, and a management plan.

Patient information

You are an 89-year-old woman who has had numerous falls bringing you into hospital over the past year, often with diagnoses of urinary tract infections. You feel that your legs just give way. You are generally more rigid and your family has noticed that you tend to shuffle along with small steps. You are generally slower. On this occasion you find it difficult to mobilise. You are a little more forgetful. You have a history of hypertension. You have no pain. Your daughter is with you. You are both worried that you keep falling although expect that another urinary tract infection is to blame.

Focused history and examination

Initial history

- Ask about duration of symptoms of falling.
- Ensure that there is no pain on this occasion suggesting a fracture (e.g. hip, pubic ramus, humerus).
- Ask about weakness and rigidity and slowing up (or down!)
- Ask about walking.
- Ask about memory and if there has been any forgetfulness.
- Ask about past medical history and drug history, noting the hypertension.

Initial examination

- Examine gait if she is able and agrees.

Further assessment

- Consider all causes of falls. The rule is that multiple causes are likely in any individual and if you find one, do not stop there but look for the next. In a frail older person insidious brain failure will collude with diminution of all facets of the neuromuscular system including sensory organs, and generalised sarcopenia.
- A test of cognition – abbreviated mental test score (AMTS) or mini-mental state examination – is useful, and here a modified AMTS should suffice.
- Take a brief social history.
- Explore concerns.

Feedback to patient

> I am not exactly sure just yet what is causing you to fall. But one of the concerns I have is that you have been becoming less able to use your legs properly over a considerable period of time. It may be that some hardening of the arteries in the brain is contributing in part to your tendency to balance trouble, and it may be that other factors are at play, too, such as nerves and muscles and joints generally becoming less efficient than they once were. And I am a little concerned to hear that your daughter feels that your memory is not as sharp as it used to be. I think at this stage we should keep an open mind and arrange a series of blood tests, a scan of the brain and a test of the memory. I also think we should ask our physiotherapists and occupational

therapists to assess your walking and balance and your overall safety on your feet. We should think, too, about whether or not we might build in some protective treatment for the bones to reduce any risk of fracture in the event that you were to fall again. I'd be happy to answer any questions you may have.

Feedback to examiners

Summarise the key history and examination findings

This woman has gait disturbance with an upright shuffling gait and some memory disturbance, and a history of hypertension.

Provide a diagnosis or differential diagnosis with supporting evidence

She probably has subcortical vascular disease/dementia [Fig. 5.102, Box 5.68].

Outline an investigation and management plan

She should have a brain scan, a blood confusion screen (blood count, routine biochemistry, calcium, thyroid function, B12), a formal mini-mental state examination and a multifactorial multidisciplinary falls assessment including a physiotherapist assessment. Assessment of home circumstances by an occupational therapist and early involvement of the memory team are important.

Box 5.68 **Subcortical vascular dementia (subcortical VaD)**

What subcortical VaD is

Subcortical VaD is a predominantly microvascular brain disease that has profound effects on gait and ultimately cognition.

Why subcortical VaD is important

Subcortical VaD is a hugely underappreciated and ill-understood and yet exceedingly common 21st century health-care problem. It is one of the commonest reasons for admission (as 'off legs' or 'collapse') to medical assessment units and for delay in discharge from hospital. Despite this, formal recognition of this problem has not occurred, and patients continue to be diagnosed with alternative diagnoses such as urinary tract infections.

Whilst dementia due to Alzheimer's disease and other dementias including other forms of VaD has attracted prominent attention, subcortical VaD has not. Unlike strokes (macrovascular brain disease), more insidious small-vessel brain disease has received less attention. And yet microvascular disease in other organs is widely appreciated. Chronic kidney disease (CKD), usually due to underlying vascular disease from hypertension or diabetes, is greatly understood, and CKD is even staged, and this underlying kidney vulnerability is often a background factor in episodes of acute kidney injury. Acute coronary syndromes often arise from chronic atherosclerotic disease. Yet the notion of brain vulnerability from underlying chronic microvascular brain disease is not widely recognised. The concepts of chronic kidney disease and heart failure are routinely appreciated, but the concepts of chronic brain disease and brain failure are given little emphasis, especially in older people with gait disturbance. When an older person falls, attention is rightly given to any comorbidities, drugs and environmental factors, and the legs are often examined to exclude musculoskeletal causes and injury. Urinalysis and heart and chest examination are often undertaken, but seldom consideration of brain disease. This is analogous to examining the wheels of a car that are not turning, without considering that the problem might have arisen at a higher control level.

Why subcortical VaD is underappreciated

- Subcortical VaD is characterised by early gait disturbance and falls, and cognitive disturbance tends to be apparent later, and because the concept of a dementing process is almost universally one of cognitive disturbance, when people present with a gait problem or falls a brain problem is understandably seldom considered.
- Subcortical VaD has become an accelerated problem as the population demographic has shifted to a much larger group of older people (notably those over 85 years of age).
- Subcortical VaD is not necessarily an easy disease to grasp without understanding the underlying pathology, the location of pathology and the clinical features that arise from that pathology.

What we mean by 'subcortical'

Subcortical literally means 'beneath the cortex', like the core of an apple. White matter tends to predominate in these areas. 'Subcortical' refers to deep brain structures where there is much white matter with aggregates of grey matter.

White matter comprises bundles of myelinated nerve cell processes (axons) which connect areas of grey matter (nerve cell bodies) of brain to each other, carrying insulated nerve impulses rapidly between neurons. Whilst grey matter can be thought of as the computing areas of the brain, white matter represents the networks of cables connecting these. The brain can adapt somewhat to white matter damage by finding alternative routes. White matter forms the bulk of the deep parts of the brain, and parts of the spinal cord. Aggregates of grey matter such as the basal ganglia (e.g. caudate nucleus, putamen, globus pallidus, subthalamic nucleus) and brainstem nuclei (red nucleus, substantia nigra, cranial nerve nuclei) are spread within white matter.

Subcortical areas include:

- Components of the forebrain including the basal ganglia (motor control), thalamus (relay station for sensory information), limbic system and hypothalamus
- Components of the midbrain including the superior and inferior colliculi involved with eye movement and localisation and hearing, and the red nucleus, which aids motor control
- Components of the hindbrain, including the cerebellum, pons and medulla.

Pathology in subcortical VaD

With ageing, loss of tissue density in grey matter (polioaraiosis) and white matter (leucoaraiosis) reflects neurodegenerative change, and

Box 5.68 **Subcortical vascular dementia (subcortical VaD)—cont’d**

progresses concurrent with decline in brain perfusion. Rates of polio- and leucoaraiosis accelerate after age 60, correlating with cortical and subcortical atrophy and ventricular enlargement. In particular, leucoaraiosis correlates with advancing age, hypoperfusion of white matter, and cognitive impairment. Leucoaraiosis is detectable in some older ‘normal’ subjects but virtually always present in VaD, and normal subjects destined for later cognitive decline may have early excessive leucoaraiosis.

Pathophysiology of subcotrical VaD – lacunar state and arteriosclerosis (Binswanger’s disease)

VaD refers to a broad category of cognitive decline attributed to cerebrovascular disease. Dementia may occur in approximately one-quarter to one-third of stroke cases. Strategic infarcts in critical areas (e.g. hippocampus, thalamus and caudate nucleus), and intracranial haematomas or mixed forms of VaD are well recognised. Subcortical VaD is due to subcortical ischaemic vascular disease (SIVD). Small-vessel disease and hypoperfusion result in focal and diffuse ischaemic white matter lesions and incorporate two pathophysiological mechanisms:

- Occlusion of an arterial lumen leading to complete infarct (lacunar infarct, often with lipohyalinosis or micro-leakage of blood) with disruption of a neural pathway
- Critical stenosis and hypoperfusion of multiple arterioles (arteriosclerosis or hypertensive microangiopathy) resulting in widespread areas of incomplete infarction of the deep white matter and consequent functional disruption of neural networks.

The end stages of the two pathways are the lacunar state and Binswanger’s syndrome, which, in practice, usually converge. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare, familial cause of SIVD in a younger age group, often with migraine history.

Clinical features of subcortical VaD and how these are explained

‘Subcortical’ areas relating to subcortical VaD

Various subcortical structures, including long motor and sensory tracts in transit between cortex and brainstem, and the extrapyramidal system, which aids smooth motor output (and the cerebellum and thalamus, which aid smooth sensory input), generally become ‘moth-eaten’ by small-vessel disease. This leads to impaired neuronal information exchange between the outside world (via long tracts and cranial nerves) and the cortex. All parts of the body are represented cortically in the homunculus – face, arm and leg, for example, interestingly upside down and present in all animals, and so a little dormouse has a tail up at the top and snout down below. There is both a motor and sensory homunculus bilaterally, the motor predominantly in the posterior frontal lobes and the sensory in the parietal lobes. The following analogy may be useful:

- Motor fibres start as millions of little roads in the cortex which join bigger highways as they descend downwards, eventually converging onto a motorway within the subcortex and internal capsule, before continuing their journey through the brainstem to supply the contralateral face, trunk and limbs.
- Sensory information, conversely, enters the brainstem and ascends through subcortical areas like the thalamus before being relayed onwards to the sensory areas of the cortex.
- We can think of strokes as macrovascular events, destroying large areas of cortex (total anterior circulation strokes) and so lots of little roads (plus optic pathways and higher cortical areas), smaller areas of cortex (partial anterior circulation strokes), subcortical areas (lacunar strokes) or brainstem. Strokes in the subcortex are commonly asymptomatic but may cause complete closure of the motorway – unilateral weakness or sensory loss – if affecting the internal capsule or thalamus. But multiple areas of microvascular damage in the subcortex from lacunar infarcts or arteriosclerosis produce a situation analogous to snow or ice on these motorways. Unless there is a pivotal motorway cerebrovascular ‘accident’, traffic is sluggish but does not stop unless the snow is intense (analogous to chronic kidney disease rather than acute kidney injury, or chronic angina rather than an acute coronary syndrome).

Clinical features of subcortical VaD

Subcortical VaD therefore gives rise to the groups of clinical features in Table 5.56 and Fig. 5.102 – neurologically, a little of everything and not much overtly of anything. Clinical features are often insidious and significant decline over months once subcortical VaD is recognised is often the tip of a much longer developing iceberg – often a history of progressive gait problems and short-term memory loss over a few years, but gait disturbance tends to precede cognitive disturbance. In the author’s experience the mean age of recognition of this type of dementia is 88–89 years.

There is no definition or set of criteria for diagnosing subcortical VaD. Cerebrovascular disease is common in older people and causes heterogeneous impairments, which range in severity. Definitions of cerebrovascular cognitive impairment are hampered by the fact that cerebrovascular disease is not easily linked to cognitive syndromes either clinically or pathologically and the presence of coincident Alzheimer’s pathology is common. Furthermore, there are no universally accepted diagnostic criteria for Alzheimer’s dementia and many proposed ones for other forms of VaD; these tend to be used in research but not in clinical practice.

Why these features are not Parkinson’s disease

These patients are slow and rigid and so it is commonly suggested that they might have Parkinson’s disease (PD). In fact subcortical VaD embraces what used to be known as vascular Parkinsonism. Here are four differences from PD:

1. Older age (average age of onset of PD 63)
2. Leg failure more than arm failure (PD patients have arm problems more than leg problems and do not present ‘off legs’ until many years down the track), with an upright rather than stooped shuffling posture
3. Symmetry (PD patients have asymmetric disease)
4. Non-sustained response to levodopa (if tried).

Furthermore, despite traditional thinking, subcortical VaD is much more common than PD. If subcortical traffic is slow in subcortical VaD, and the legs are affected more than the arms, one might ask why in PD the arms are affected more than the legs (albeit all four limbs being affected to some degree in both conditions). One thought is based on primate evolution – that swinging and fine motor control in the hands and arms is more important than walking. If this is so, then one might expect the arms to fare worse in PD – largely an extrapyramindal biochemical disturbance, and one might expect the legs to fare worse in subcortical VaD because upper limb nerve fibres would have a more

Box 5.68 **Subcortical vascular dementia (subcortical VaD)—cont'd**

generous blood supply. Of course another reason is that subcortical VaD is not a direct replacement in terms of location to PD but with different pathology, but rather may affect areas of gait control unaffected in PD. We simply do not know.

Subcortical vascular disease versus normal ageing

Neuroimaging often shows small-vessel disease and atrophy, often reported as normal for age. But this is not so. What we are seeing is chronic brain disease, potentially ultimately leading to brain failure. This is no difference in importance from conditions we recognise routinely such as CKD and heart failure and, even where asymptomatic, we would not refer to stage 2 CKD or a reduced cardiac ejection fraction as normal. We might say these features are not unexpected for age, but that is not the same as saying they are not pathological, and these features are by no means inevitable with age and the causes might be modifiable.

Treatment for subcortical VaD

There is no theoretical reason why risk factor intervention, notably treating hypertension, might not offer benefits that are preventive or delay progression, for both gait and cognitive features, but research is lacking. Diagnosis enables appropriate involvement of the multidisciplinary team. Diagnosis is important to patient and family, as is appreciation that preceding non-cognitive problems such as gait disturbance and falls are part of a dementia process before cognitive disturbance prevails. This allows advance planning of care and personal affairs. Recognising and sharing with the patient and family that consequences of dementia such as muscle wasting, falls, poor nutrition and pneumonia may be explained by brain disease, rather than being the prime reasons for decline in a health-care setting, is vital.

Important tips

Tip 1: Use precise terminology – not 'off legs' or 'collapse'

These are imprecise terms, and never diagnoses. It may be useful to consider 'off legs'/collapse within a 'falls – unable to stand' diagnostic framework.

Tip 2: Have a differential diagnosis list for falls

Falls may occur without or with loss of consciousness (often syncopal). Most falls are without loss of consciousness and in older people multifactorial, with both intrinsic and environmental factors at play. Clinicians should consider whether features of subcortical VaD are present.

Tip 3: Appreciate the role of the brain in 'off legs' patients

Urinary infections and other 'simple' diagnoses should not be applied liberally without appreciation of what else might be going on. It is implausible that a positive urine dip without symptoms, without evidence of systemic upset and without a rise in inflammatory markers could produce falls, substantial confusion or loss of consciousness.

Tip 4: Appreciate what dementia means

- The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia refer to memory impairment and at least one other cognitive disturbance (aphasia, apraxia, agnosia, executive dysfunction) which significantly impairs social or occupational activity. But in essence dementia is brain failure, with disturbance of all the brain does.
- We can classify dementia by cause.
- We can classify dementia by anatomical area. Alzheimer's dementia tends to start in the medial temporal lobes with early memory loss, and later progresses outwards and forwards to parietal lobes (producing task problems or apraxias, recognition problems or agnosias, and visuospatial problems) and ultimately frontal lobes causing executive dysfunction and behavioural problems. In much VaD and frontotemporal dementia disease starts more frontally, with greater behavioural disturbance.
- We can classify dementia, especially vascular, as cortical or subcortical.

Tip 5: Be aware of the clinical features of subcortical VaD

Be aware especially of the patient with an upright shuffling gait, poor facial expression and apathy.

Tip 6: Be aware of subcortical dementia versus cortical dementia

Subcortical dementia and cortical dementia occur within an overlapping spectrum. But just as we have the concept in delirium of hypoactive and hyperactive patients, and though a simplification, dementia often produces the pattern of the 'frozen' patient or the 'wanderer':

Frozen (often subcortical disease)

- Legs sluggish (slow motorway traffic)
- Relative preservation of cognition
- Therefore 'physically fragile but cognitively agile' (the 'frozen')

The wanderers (often cortical disease)

- Cognitive areas affected early
- Legs 'ok' (some minor roads rather than motorway affected)
- Therefore 'cognitively fragile but physically agile' (the 'wanderers')

Tip 7: Think…!

Having good differential diagnosis lists is one of our pivotal skills, allowing us to put symptoms into plausible diagnoses and therefore create appropriate investigations to further the diagnosis and so implement appropriate treatment and actually help the patient. Otherwise 'off legs'/collapse will become a diagnosis rather than a presenting complaint and the terribly tiresome triad of 'troponin, 24-hour tape and trimethoprim' will be a convenient management strategy.

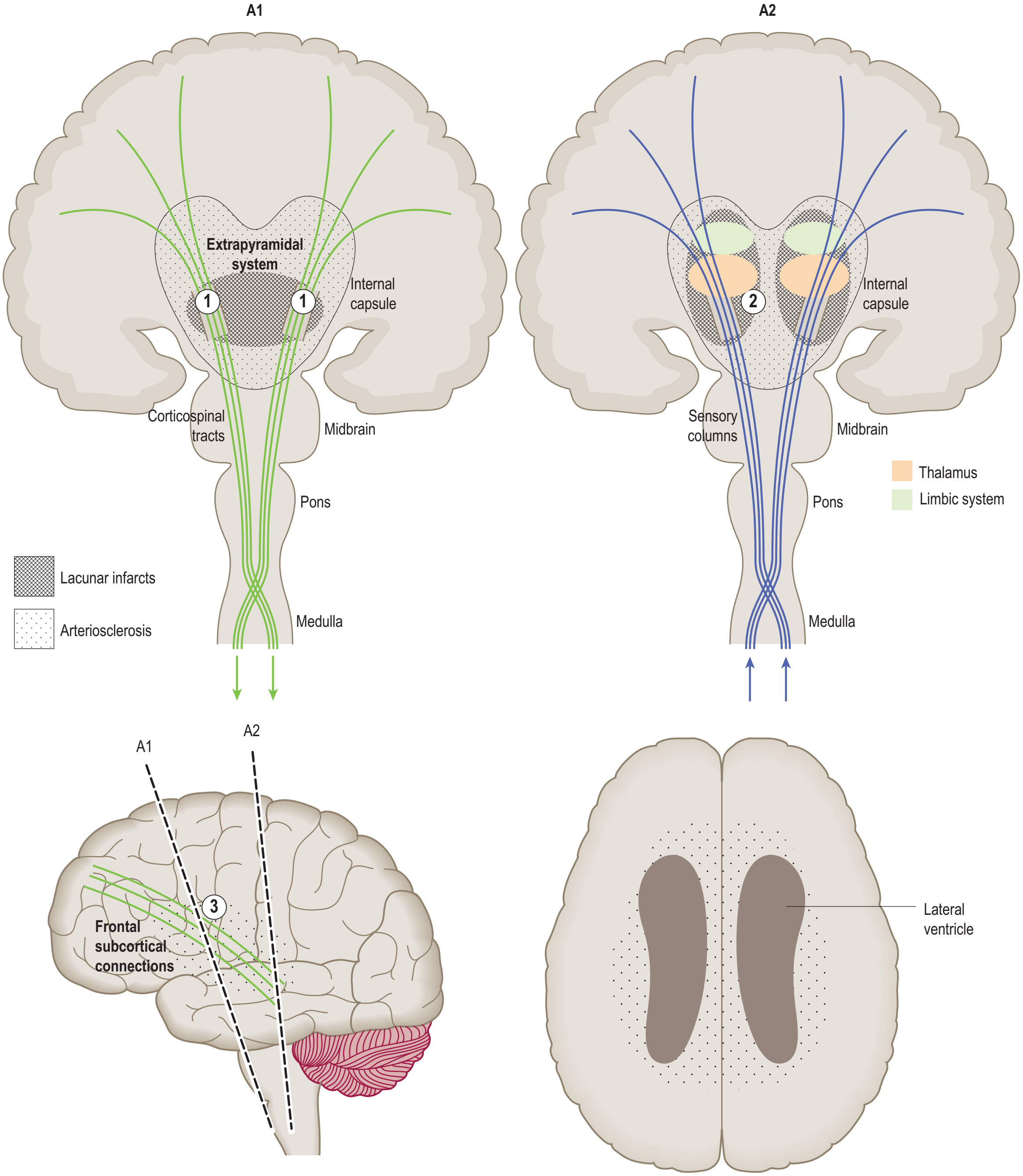

A1
A2
Extrapyramidal system
1
1
Internal capsule
Corticospinal tracts
Midbrain
Pons
Medulla
Lacunar infarcts
Arteriosclerosis
2
Internal capsule
Sensory columns
Midbrain
Pons
Medulla
Thalamus
Limbic system
A1
A2
3
Frontal subcortical connections
Lateral ventricle

Figure 5.102 Subcortical vascular dementia (numbers 1, 2 and 3 refer to Table 5.56).

Table 5.56 Clinical features of subcortical vascular dementia (VaD)

Groups of clinical features		Explanation and notes
1. Weakness and rigidity with prominent gait disturbance	An upright 'marche a petit pas' gait with small, shuffling steps may occur ('vascular Parkinsonism') before mobility stops altogether (an 'off legs' scenario)	The critical mass of long motor tracts damaged is sufficient to produce generalised weakness but insufficient to produce overt focal upper motor neuron signs of pyramidal weakness (all motorways on all routes are 'narrowed to one or two lanes' in subcortical dementia rather than completely blocked on one route as in a stroke) This, in concert with wider subcortical damage including damage to basal ganglia, produces gait disturbance
	Rigidity (and facial hypomimia)	Some rigidity is present due to extrapyramidal damage, similar to that seen in Parkinson's disease, although Parkinson's disease has a unique pattern of progression and tends to affect a younger age group
2. Additional features that may be present	Sensory impairment	Just as motor information is slowed from the brain, so may be sensory relay to the brain via the long sensory tracts and thalamus
	Pseudobulbar dysarthria and swallowing problems with risk of aspiration (especially later stages)	Supranuclear connections to cranial nerves may also be affected, including corticobulbar tracts
3. Cognitive disturbance	Bradyphrenia (slowness and rigidity of thinking) Executive dysfunction (difficulty planning, organising and sequencing); difficulty in tasks requiring mental manipulation, e.g. arithmetic, comprehension of complex syntax, reversing digits or other sequences such as months of the year Apathy Forgetfulness (but amnesia is not a strong feature)	Cortical anatomy is relatively spared early on (although there may be coexisting cortical VaD) but subcortical structures aid, through subcortical–cortical (notably frontal lobe) connections, cognitive tasks Neuropsychological assessment reveals a subcortical deficit and although subcortical VaD may superficially resemble a frontotemporal dementia the presence of subtle neurological signs, the absence of predominant personality change and relative preservation of insight differentiate it

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Appendix – 100 tips for passing PACES

BEFORE PACES

Timing

1. Many candidates feel that MRCP exams should be sat (and failed) as often as possible in the belief that passing will be the reward of negative but repetitive experience! With the right preparation you can easily pass PACES. Take it when you feel ready and do not listen to pessimistic colleagues.

What the examiners are looking for

2. The examiners want to be satisfied that you are a safe, competent doctor, suitable to enter specialist training.
3. They are not looking for specialist knowledge.
4. They are not looking for the next Professor of Medicine.
5. They want to know that, as your general medical consultant, they could have a sensible discussion with you about the care of a patient.
6. They want to know that, as your consultant, they could entrust the care of their patients to you when away from the wards.
7. They respect a friendly and confident manner, but not arrogance.
8. Many candidates adopt 'victim mode' with head down and victim posture throughout PACES. This concerns examiners, who wonder how a nervous candidate might cope in an emergency. Examiners are likely to be more impressed by the candidate who stands with an upright, confident posture, hands by sides or behind back, and makes good eye contact.

It's in your hands!

9. Passing PACES is well within your grasp.
10. The idea that passing is in your examiners' hands is a negative one.
11. It is in your hands!
12. You can pass with the right preparation.
13. Success is about discipline and desire. You must work to pass, and want to pass.
14. Passing is easier than you think and you probably need to know less than you think. Reading larger textbooks is not a good use of time. Seeing patients is.

Practice

15. Most candidates are competent enough to pass PACES by the exam date. Invariably lack of confidence is the problem. The aim of practice is to build a natural confidence into your already adequate competence.
16. Practise your examination technique for each system at every opportunity (whenever possible in front of senior colleagues).
17. Practise the history-taking skills taught in this book with patients at every opportunity.
18. Practice your communication skills at every opportunity. As well as discussing management and ethical dilemmas with patients and colleagues, some candidates find it helpful to form discussion groups.
19. Be alert to any topical issues in the news and in general medical journals that could be examined and discussed.
20. Read widely. Reading strengthens your communication prowess.
21. Practice does not automatically make perfect. Perfect practice does!

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22. When you go into the exam you should appear as though you have performed your examination of each system hundreds of times before, ideally because you have!

ON THE DAY OF PACES

Some formalities

23. PACES requires sustained energy and you must not be so tired through stress and studying as to lose momentum on the day. Meerkats get plenty of sleep each night to be alert and vigilant each day! Try not to work continuously in the run-up to PACES. Have some early nights and avoid caffeine and alcohol.
24. Dress professionally.
25. Arrive at the exam venue in good time.
26. Take your stethoscope. Other equipment should be provided but you may prefer to carry your own ophthalmoscope, tendon hammer and red pin. A case of 'James Bond' gadgets will not impress examiners.
27. Thank your patients and examiners after each case.

At the start

28. Keep in mind that there should be nothing particularly rare and therefore nothing to be particularly scared of throughout the five stations. However, even good candidates find some cases much more difficult than others. A few poor performances can still mean an overall pass and you should be determined from the start to put any difficult cases behind you and give the next one, with different examiners, your best shot.

The patients are more important than the examiners!

29. The patients are your prime concern. Thinking that the outcome of the exam is in the hands of the examiners is not helpful. The examiners will pass or fail you on the strengths and weaknesses of your performances with patients. Focus on your patients and the exam will take care of itself.
30. Do not hurt patients on any account! This is one of the easiest ways to fail PACES.
31. Be considerate to patients. This is one of the easiest ways to pass PACES. It may seem obvious, but the notion of treating other people as we would like to be treated ourselves is a remarkably effective guiding principle in PACES, as it is in medical practice.

Examiners

32. Examiners come with the full range of personalities. The best advice is not to worry about what sort of examiners you get. Focus instead on doing what you do as well as you can do it.
33. The examiners are not trying to catch you out but want to find out what you know.

Examining patients

34. Be nice to patients! This is worth reiterating. Treat them with respect at all times. A considerate (but not obsequious) approach to patients is the single biggest determinant of success.
35. Ask each patient for permission to examine and if they are in any pain.
36. Ensure that each patient is positioned correctly before you begin.
37. Observation is a vital part of examination!
38. Don't wait for the examiners to keep telling you what to do. Do it spontaneously, using the *Recognition–Interpretation–Discussion (RID)* sequence.
39. Don't look for feedback from the examiners. You will not get it, and looking for it will unnecessarily unnerve you. A good candidate, without appearing to rush, will elicit signs and gather information considerately, swiftly and spontaneously.
40. Remember that you are 'on stage'. Let the examiners see your performance. As in a driving test, your actions should be natural but clearly visible.
41. Remember that from the examiner's perspective you do two things in each case. Firstly, you *examine* your patient. Secondly, you *present* your findings. From your perspective, you are doing much more. While examining, you are looking for signs, deciding how best to interpret these and thinking about how you are going to present your findings. A structured approach is essential. The examination schemes in this book can be performed automatically with practice, allowing you to concentrate on recognising and interpreting signs and to use this same framework for presenting.
42. At the end of each case ensure that your patient is as comfortable as you found them.
43. Don't forget to thank them.

Examining and presenting

44. Avoid the 'running commentary' approach. Many candidates wonder if they should 'talk as they go' or 'present their findings at the end'. Some candidates believe the running commentary a way of scoring points – such that even if their final diagnosis is incorrect, they may at least have reported some correct findings. This is risky.
45. A running commentary slows you down and fragments the smooth flow of your examination. Examiners do not want to be told that you are examining the pulse to check whether it is collapsing. They want to see you doing it. Examiners are human and easily bored. They will

forgive you for omitting things here and there but may be irritated if you do not 'just get on with it'. Constant stops and starts are more likely to draw the attention of examiners to mistakes. Conversely, candidates with competent examination skills who 'get on with it' tend to impress examiners, often lulling them into a sense of security – switching them from hawk to dove mode and blinding them to mistakes.

46. Talking while examining interferes with your *rapport* with a patient. You may think rapport is something you cannot develop within a few minutes but patients in PACES generally have a very good idea of how well a candidate performs, simply because what impresses patients is what impresses examiners – a natural, considerate and considered approach. Be attentive to your patient, not the examiners, while examining. Be completely absorbed by your patient. Tell them what you are doing as you are doing it, smile, look and listen for the subtle cues of cooperation, and above all show that you care. Rapport will come naturally and your examiners, at this stage, should fade into the background.

47. The 'absence' of the examiners allows you to pool all of your mental energy into the case, and should reduce anxiety.

48. The opposite applies when presenting your case. Be decisive in finishing your examination and politely turn away from your patient to give your undivided attention to the examiners. At this point, some candidates are so relieved if they have a diagnosis that they blurt it out and wait for feedback – 'Graves' disease!' Talk through the *Recognition–Interpretation* sequence instead.

49. When presenting, avoid lots of 'ums' and avoid reporting lists of negative findings.

50. Conversely, if you have elicited a sign, mention it. Candidates surprisingly often fail to mention signs they have clearly elicited. Do not assume the examiners know that you have elicited a sign.

51. Never make up signs to conform to an anticipated diagnosis. It is a sure way to fail.

52. If you know the diagnosis, state it and then give the relevant supporting findings.

53. If you do not know the diagnosis, describe what you found.

54. The key to impressing examiners is in ever striving 'to go further'. Examiners prefer candidates who spontaneously present their findings and thoughts.

55. Candidates who lack confidence often look back at their patient when presenting or asked questions as if the findings or answers will magically appear. Try to avoid this.

56. Avoid uncomfortable silences (where no marks can be awarded) by saying something intelligent. For example, if you find a mass in the left upper quadrant and are not sure if it is a spleen, you could describe findings you might expect in support of it being a spleen and findings you might expect in support of it being a kidney. You could also suggest an ultrasound scan to resolve the uncertainty.

57. The key is to try to keep talking, and saying sensible things.

When the diagnosis is not clear

58. Don't always expect a full house of signs. Patients are not from textbooks and examiners frequently disagree about signs before the exam starts. Try to keep calm. Simply blurting out a diagnosis about which you are unsure is hazardous. Remember that describing your findings, even if your diagnosis is incorrect, will allow points to be awarded.

59. There will always be cases where the diagnosis is not clear. Report your findings, telling the examiners which other signs you might have expected to find in support of the important differential diagnoses and what else you could do to resolve the uncertainty. Examiners seldom fail candidates who can demonstrate logical approaches to dilemmas. What often happens is that candidates fail themselves by 'going blank' when they are uncertain.

60. *PACES for the MRCP* has tried to strike a balance between structure and flexibility. It provides a framework for diseases likely to be encountered in PACES, but every patient is different. The same disease is exhibited in different ways in different patients and its impact is individually determined. You should tailor your knowledge to specific patients. *PACES for the MRCP* is not a substitute for seeing as many patients as possible on the wards, and *Recognition–Interpretation–Discussion* is not something to which you need always adhere. It is simply a map to guide you through cases and bring you back on course if things go wrong.

61. Remember that 'common things are common'. You will have seen most things before.

62. Remember that double pathology can occur.

63. Diagnoses can be difficult. Many candidates struggle especially with neurology and heart valve cases. In cases where you are unsure:
  (i) Describe what you found. Be honest. Never make up signs.
  (ii) Tell the examiner two or three differential diagnoses.
  (iii) Describe what else you might have expected to find in support of these.
  (iv) State some things you could do to help resolve the issue, e.g. dynamic auscultation, arrange echocardiogram.

64. Before this point, many candidates have failed themselves, believing the signs too confusing and their diagnosis to be wrong. Practice often falls far short of theory.

History-taking skills

65. Use the history-taking skills described on Station 2.

Communication skills

66. Awareness of the history-taking and communication skills described in this book allows you to further improve your history-taking and communication skills.
67. Watch good communicators at work. See how they handle situations.
68. Try to bring discussion with examiners to life. Add sparkle by appearing enthusiastic and interested in the topic for discussion.
69. Watching politicians and debate programmes on television is a way of seeing negotiation at work. You do not have to like the politicians or agree with their arguments but take an interest in how they communicate. They are usually effective speakers.
70. Remember that we are all more similar to each other than we are different. We share the same molecular ingredients, separated only by a twist of the genetic kaleidoscope! It is never hard to imagine ourselves in other people's shoes. If all the lessons you have learnt seem hard to remember, then one guiding principle should ensure that you never stray from the right ballpark – that of asking yourself what you would want if you were in your patient's situation.

Answering examiners' questions

71. Listen to the question!
72. Answer the question asked!
73. Try not to repeat the question asked!
74. Take a moment or two before answering it.
75. Look at the examiner and not at the floor. Eye contact is very important.
76. Try to appear confident, yet reflective, giving a well-structured answer. Your examiners will be as impressed by your communication skills as your knowledge.
77. Speak clearly and succinctly. Try to avoid speaking too quickly, and rambling.
78. Some candidates speak very quietly. It is unusual for candidates to speak very loudly. Unless you are one of the latter, it may help to speak up slightly, more *authoritatively*.
79. Do not think of the examiners as examiners. This is easier said than done. Try to think of the examiners as colleagues with whom you are discussing interesting ward cases. Some candidates find it helpful to imagine themselves on a ward round.
80. Curiosity keeps us alert. Let your enthusiasm, curiosity and interest shine through.
81. Difficult questions often reflect a good performance. Examiners will challenge and probe and sometimes make you feel uncomfortable or inadequate.
82. Be confident, if you think you are right, but never argue!
83. Be confident, not arrogant.
84. Avoid casual phrases and abbreviations.
85. Avoid emotive words like 'tumour' in front of patients.
86. Do not be afraid to retract statements you feel are wrong.
87. If you do not know the answer to a question, be honest in your ignorance.
88. Above all, avoid saying anything that would pose a danger to patients.
89. Remember that examiners' questions are often not predetermined but built around what you tell them – 'Would you like to explain that?' You have some opportunity to take control of the areas to be discussed.

Answering examiners' questions at the communication skills and ethics station

90. Don't be too dogmatic. It can be dangerous to go down one route when discussing ethical dilemmas. It is wiser to state the broad range of issues an ethical dilemma creates, and that there are often numerous viewpoints to consider.
91. Remember that you are not expected to have all the answers. Examiners may be impressed by a mature attitude of self-awareness and a need to discuss an issue further with colleagues, a medical defence organisation and so on. Willingness to communicate with colleagues is considered a strength.
92. While there is often no right or wrong answer, you can state what you think is the best course of action. Examiners may challenge you but it does not mean that your argument is flawed. Provided you feel that your argument is 'safe', run with your convictions. The examiners are usually checking for consistency of your argument, ensuring that it is genuinely your belief, and that you can justify it.
93. Sometimes examiners' questions will be hard! They may be searching, probing and uncomfortable. Again, this does not necessarily mean that you are doing anything wrong. It may mean that you are performing well.
94. Try to be 'patient centred' in your responses.

When you think things are going badly

95. Do not expect feedback from your examiners. They do not give it. This said, a confident, respectful and competent candidate with a friendly but not overly familiar manner is someone examiners warm to immediately.

96. Difficult cases may be genuinely difficult to all candidates (and to examiners!).
97. Difficult questions often reflect a good performance!
98. Examiners may play on your nerves and ask 'Are you sure?' in response to your answers. Often, they are simply testing your confidence and your answer is correct.
99. Each station and case is marked separately. Try not to lose hope if you feel you have performed badly in a particular case. Examiners allow numerous mistakes (provided these would not have overtly dangerous clinical consequences) and a poor performance does not necessarily result in overall failure.

AFTER PACES

100. Most candidates who pass do so despite a few weak performances. Many candidates are convinced that they have failed until they receive the 'Pass' envelope from the College. That is the time to put PACES behind you, watch a movie and relax.

Index

Page numbers followed by ‘f’ indicate figures, ‘t’ indicate tables, and ‘b’ indicate boxes.

Notes
- vs. indicates a comparison or differential diagnosis.
- To save space in the index, the following abbreviations have been used:
  - ACE – angiotensin-converting enzyme
  - AIDS – acquired immunodeficiency syndrome
  - ARBs – angiotensin II receptor blockers
  - COPD – chronic obstructive pulmonary disease
  - CT – computed tomography
  - ECG – electrocardiography
  - HIV – human immunodeficiency virus
  - MRI – magnetic resonance imaging
  - NHS – National Health Service
  - NICE – National Institute for Health and Clinical Excellence

A

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